SECONDARY PREVENTION METHODS AFTER ACUTE MYOCARDIAL INFARCTION AMONG MEDICARE BENEFICIARIES

Montika Denise Bush

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Approved by:

M. Alan Brookhart

Anna Kucharska-Newton

Gang Fang

Ross J. Simpson, Jr.

Til Stürmer

ABSTRACT

Montika Denise Bush: Secondary Prevention Methods after Acute Myocardial Infarction among Medicare Beneficiaries
(Under the direction of M. Alan Brookhart)

Objective: To describe the use of secondary prevention methods and to investigate the effect of cardiac rehabilitation (CR) initiation on hospitalization following myocardial infarction among older adults.

Methods: Medicare beneficiaries having a myocardial infarction (MI) in 2008 and survived to discharge were eligible for this study. In aim 2, beneficiaries also had to survive 60 days post discharge and have a revascularization procedure during hospitalization. Competing risk analysis was used to estimate the cumulative incidence of adoption of secondary prevention recommendations such as initiating cardiac rehabilitation and the difference in the cumulative incidence of subsequent hospital admission between cardiac rehabilitation initiators and non-initiators.

Results: At 30 days post-MI 6.7% (95% CI: 6.5%, 6.8%) of beneficiaries included in aim 1 initiated cardiac rehabilitation and 14.2% (95% CI: 14.0%, 14.5%) initiated by 1-year post-MI using competing risk analysis. From the Kaplan-Meier analysis, 6.9% (95% CI: 6.7%, 7.0%) and 15.1% (95% CI: 14.8%, 15.3%) of beneficiaries initiated cardiac at 30 days and 1-year post myocardial infarction respectively. Overall 4.5% (95%CI: 4.4%, 4.6%) of patients died by 30 days post myocardial infarction rising to 17.0% (95%CI: 16.8%, 17.3%) at 1 year post myocardial infarction. At 1-year post discharge, cardiac rehabilitation initiators in aim 2 had a

lower risk of recurrent MI (4.2% 95%CI: 3.5%, 5.1%), cardiovascular (15.7% 95%CI: 14.3%, 17.2%), and all-cause (30.4% 95%CI: 28.8%, 32.1%) hospitalization than non-initiators (18.0% 95%CI: 17.6%, 18.4%; 33.2% 95%CI: 32.5%, 33.8%).

Conclusions: Cardiac rehabilitation participation was low in Medicare beneficiaries. Outpatient cardiac rehabilitation was associated with a reduced risk of recurrent myocardial infarction, cardiovascular disease, and all-cause hospital admissions 1-year post discharge in older myocardial infarction survivors.

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To all of the prayer warriors who stood with me during this process and to the God we serve, thank you.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AACVPR	American Association Of Cardiovascular And Pulmonary Rehabilitation
ACC	American College Of Cardiologist
ACE	Angiotensin-Converting Enzyme
ACS	Acute Coronary Syndrome
AHA	American Heart Association
ARB	Angiotensin Receptor Blockers
ATC	Anatomical Therapeutic Chemical
BB	Beta Blocker
BMI	Boday Mass Index
CABG	Coronary Artery Bypass Graft
CCU	Cardiac Care Unit
CCW	Chronic Condition Warehouse
CHD	Coronary Heart Disease
CI	Confidence Interval
CIF	Cumulative Incidence Functions
CMS	Centers For Medicare And Medicaid Services
CPT	Current Procedural Terminology
CVD	Cardiovascular Disease
DAG	Directed Acyclic Graph
ECG	Electrocardiogram
GRACE	Global Registry Of Acute Coronary Events
GRM	Guideline Recommend Medications

GWTG	Get With The Guidelines Program
HCPCS	Healthcare Common Procedure Coding System
HDL-C	High-Density Lipoprotein Cholesterol
HMG-CoA	3-Hydroxy-3-Methylglutaryl Coenzyme A
HR	Hazard Ratio
ICD 9	International Classification Of Diseases, Clinical Modification 9th Revision
ICU	Intensive Care Unit
IPT	Inverse Probability Of Treatment
IRB	Institution Review Board
KM	Kaplan-Meier
LDL-C	Low-Density Lipoprotein Cholesterol
LOE	Level Of Evidence
LOS	Length Of Hospital Stay
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular And Cerebrovascular Event
MedPAR	Medicare Provider Analysis And Review
MI	Myocardial Infarction
NDC	National Drug Codes
NOS	Not Otherwise Specified
PAD	Peripheral Artery Disease
PCI	Percutaneous Coronary Intervention
PREMIER	Prospective Registry Evaluation Outcomes After Myocardial Infarction: Events And Recovery

SD	Standard Deviation
STEMI	ST Elevated Myocardial Infarction
WHO	World Health Organization

CHAPTER 1: INTRODUCTION AND SPECIFIC AIMS

1. Overview

The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) recommends a multi-disciplinary approach for secondary prevention of cardiovascular events and death in patients with acute coronary syndromes that includes exercise training, risk factor modification, and psychosocial evaluation and counseling [1, 2]. These guidelines are implemented in practice with cardiac rehabilitation (CR) programs; however, the utilization of these programs is not well understood in the elderly [3]. Since CR clinical trials enrolled younger mostly white male participants, there exists an opportunity to understand the efficacy of these programs in older more gender diverse populations than has previously been studied. Since clinical trials and observational studies provided as support for these recommendations focused on the effects for each component individually, it is important to describe the use of these guidelines in combination in practice [1, 2]. While the clinical trials of cardiac rehabilitation focused on mortality benefits, few investigators reported the benefits of cardiac rehabilitation on specific cardiovascular or all-cause hospitalization after an MI [4, 5]. The goals of this study are to summarize the use of guideline recommendations after hospital discharge following myocardial infarction (MI) and to estimate the effects of outpatient cardiac rehabilitation on cardiovascular related hospitalizations and all-cause hospitalizations in an elderly US population. The knowledge provided by this study will inform patients, providers, and insurers about use and benefits of following guideline recommendations.

2. Specific Aims

Specific Aim 1: To describe the use of health care services related to guideline recommendations for secondary prevention of cardiac events after hospital discharge for MI among Medicare beneficiaries.

Specific Aim 2: To estimate the effect of initiation of cardiac rehabilitation services after MI on subsequent hospital admission for MI, cardiovascular related events, or all-cause admissions.

Hypothesis: Initiation of cardiac rehabilitation services within the first 60 days after MI hospital discharge will decrease the risk of subsequent hospitalization within 12 months.

Specific Aim 3: To estimate the effect of initiation of cardiac rehabilitation services after MI on subsequent hospital admission for MI, cardiovascular related events, or all-cause admissions in clinically relevant subgroups such as prescription fills for guideline recommended post-MI pharmacotherapy.

Hypothesis: There is a difference in the effect of cardiac rehabilitation initiation on subsequent hospitalization after an MI between strata.

CHAPTER 2: BACKGROUND

1. Heart Disease Burden

Although the mortality rate associated with cardiovascular (CVD) events has decreased by 30% over the 10-year period between 1998 and 2008, heart disease remains the leading cause of death in the United States with approximately 812,000 of the nearly 2.5 million deaths occurring in 2008 attributed to CVD events [6]. Rogers et al also reported that almost half of the CVD deaths (405,000) belonged in the coronary heart disease (CHD) category, a subset of the conditions used to define CVD that includes myocardial infarction. Based upon the National Health and Nutrition Examination Survey: 2005-2008, the prevalence of coronary heart disease in Americans at least 20 years old was 16.3 million people with approximately 85% being at least 60 years old [6]. Using unpublished data from the Cardiovascular Health Study and the Atherosclerosis Risk in Communities study, the American Heart Association estimates that 610,000 new and 325,000 recurrent MI events occur annually [6, 7]. History of MI is a risk factor for subsequent heart disease and recurrent attack. The percentage of people at least 65 years at the time of their first MI who will have recurrent MI/fatal CHD, heart failure, or stroke within 5 years after MI is 22%, 20%, and 5% respectively for men and 22%, 23%, and 8% respectively for women [6].

2. Medicare Insurance Program

Medicare is a governmental sponsored health insurance program for people over the age of 65, those under age 65 with specific medical conditions. Medicare coverage is comprised of four segments (www.cms.gov). Part A is hospital based insurance and Part B is provider (i.e. doctors) based insurance. Original Medicare only included Part A and B as government funded fee-for-service coverage. In 2008, enrollment in fee-for-service Medicare was high (76.4%) for beneficiaries 65 years of age and older (www.cms.gov). The remaining beneficiaries were enrolled in Medicare Part C also known as Medicare Advantage which is insurance coverage provided by government approved private insurance companies. Medicare Part D includes prescription drug coverage without respect to enrollment in either standard fee-for-service Medicare or Medicare Advantage plans. The Centers for Medicare and Medicaid Services (CMS) is the government agency responsible for governance and administration of the Medicare program including approving private insurance companies and allowing the use of the administrative claims data for research.

3. Overview of Secondary Prevention Guideline Recommendations

Based upon trials conducted in the 1970's and 1980's, early recommendations for heart attack prevention included specific recommendations for antiplatelet/anticoagulation therapy, ACE inhibitor therapy, and Beta-blocker therapy [8]. Rehabilitation that includes physical and occupational therapy was recommended as early as 1993 [9]. As new drugs came to market, they were added to the guidelines. The knowledge gained from multiple clinical trials and observational studies on secondary prevention of cardiovascular events has been synthesized into scientific statements and practice guidelines from the American Heart Association (AHA), the

American College of Cardiologist (ACC), the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), and the Agency for Health Care Policy and Research (currently the Agency for Health Research and Quality) [10, 11]. The core components of the secondary prevention guidelines include patient assessment, nutritional counseling, weight management, blood pressure management, lipid management, diabetes management, tobacco cessation, psychosocial management, physical activity counseling, and exercise training [10] (Appendix Table 1). The focus of this study is on those health care services that can be identified using administrative claims data (cardiac rehabilitation services and evidence based medications).

4. Cardiac Rehabilitation

4.1. Introduction.

In 1993, the World Health Organization (WHO) published a book that defined cardiac rehabilitation as "the sum of activities required to influence favorably the underlying cause of the disease, as well as the best possible physical, mental and social conditions, so that they may, by their own efforts, preserve or resume as normal a place as possible in the community. Rehabilitation cannot be regarded as an isolated form of therapy but must be integrated with the whole treatment of which it forms only one facet" [12]. In 1994, the American Heart Association (AHA) issued a scientific statement that similarly advocated exercise training, risk factor modification, and psychosocial counseling as the 3 main focus areas for cardiac rehabilitation in the United States [13]. Agency for Health Research and Quality (formerly Agency for Health Care Policy and Research) published first clinical practice guideline in October 1995 that recommended cardiac rehabilitation for secondary prevention.

4.2. Evidence of Efficacy.

Cardiac rehabilitation is included as a Class 1 (useful/effective/beneficial) recommendation in the AHA/ACC guidelines for the management of patients with unstable angina and myocardial infarction [1, 14]. Several meta-analyses of randomized control trials which investigated the efficacy of cardiac rehabilitation program vs. usual care without exercise published showing the protective effect of cardiac rehabilitation programs after cardiac events on mortality with at least 1 year of follow- up [4, 5, 15, 16]. The meta-analysis authors reported a reduction of 20% to 26% in all-cause mortality, 26% to 36% in cardiac-related mortality, and 21% to 47% in recurrent infarction. Meta-analysis results were statistically significant except for the intervention effect on recurrent infarction reported by Taylor et al. A large observational study of the elderly using Medicare claims data reported reductions in 5 year all-cause mortality between 21% and 34% using 3 different methods of analysis [17]. Although the results of the observational study are similar to the earlier clinical trials, the authors note there may still be residual confounding in their results. The effects of different levels of cardiac rehabilitation therapy were reported by Suaya et al and Hammill et al [17, 18]. Although each study had a different definition for dose of therapy, they both reported that more therapy resulted in greater mortality reduction. This result differs from the meta analyses by Heran et al and Taylor et al which did not find a significant difference in all-cause or cardiovascular mortality by dose of cardiac rehabilitation therapy. The conflict in results could be related to the difference in definition of dose, the difference in study population, or the effect of residual confounding in the observational studies.

4.3. Medicare Coverage.

Since 1982 Medicare has provided coverage for phase II (outpatient) cardiac rehabilitation services for beneficiaries who have had an acute MI in the last 12 months, had coronary artery bypass graft (CABG) surgery, or a stable angina diagnosis. Although Phase I (inpatient) CR is covered by Medicare while Phase III (maintenance) CR is not covered by Medicare neither are the focus of this study. Initially Medicare coverage focused on medically supervised exercise training with ECG monitoring as necessary. A policy update in 2005 (effective March 2006) added coverage for additional conditions such as heart valve repair and percutaneous transluminal coronary angioplasty and additional services such as risk factor modification education and counseling. Medicare will cover 2 to 3 sessions per week for 12 to 18 weeks up to 36 sessions without the need for special permission. [19]

4.4. Utilization.

Despite the recognized benefit by the medical community as indicated by the class 1 recommendation, cardiac rehabilitation is underutilized in the United States. An observational study of Medicare beneficiaries who experienced an acute MI or had coronary bypass surgery in 1997 reported that only 14% beneficiaries who had an MI as their index hospitalization initiated CR within the first year after their qualifying event [20]. The study investigators from a single center participating in the Get with the Guidelines program who identified acute MI patients hospitalized between 2002 and 2003 noted that only 19% of 718 patients referred to CR via the quality improvement plan protocols actually attended at least one session. [21].

Research has shown that there are both system and individual level factors that contribute to this lack of participation in CR programs. Much of the research on CR utilization has focused on how to increase referral for this service since intervention on the referral process is seen as the

rate limiting element in the utilization process. Several review articles of factors that affect CR referral identified physician preference, patient visit to a cardiologist, and access to medical insurance as system factors that positively predicted CR referral [22, 23]. These reviews also identified demographic factors such as younger age, male gender, marriage, completing high school, and English speakers as positive predictors of CR referral. The effect of race on CR referral was unclear based upon these reviews since the results in one study in each review showed race as a negative predictor while the another study in each review did not show an effect of race on CR referral. The authors in both reviews noted that patients undergoing a CABG or percutaneous coronary intervention (PCI) procedure during hospitalization as well as those patients diagnosed with hypercholesterolemia or hypertension were more likely to be referred for CR. In the analysis by Cortes et al current smoking was also identified as a predictor of CR referral but smoking status was not a predictor of CR referral by Jackson et al. Additionally Jackson et al identified physician endorsement, ease of access to transportation, proximity to facility, younger age, male gender, marriage, high education, insurance coverage, and a diagnosis of hypercholesterolemia or diabetes as positive predictors for CR use. In an analysis of the Prospective Registry Evaluation outcomes after Myocardial Infarction: Events and Recovery (PREMIER), the authors identified male gender, marriage, high education, insurance coverage, hypercholesterolemia, and higher BMI as positive predictors of CR use within 1 month of acute MI and PCI, hypertension, and PAD as negative predictors during the same time period [24].

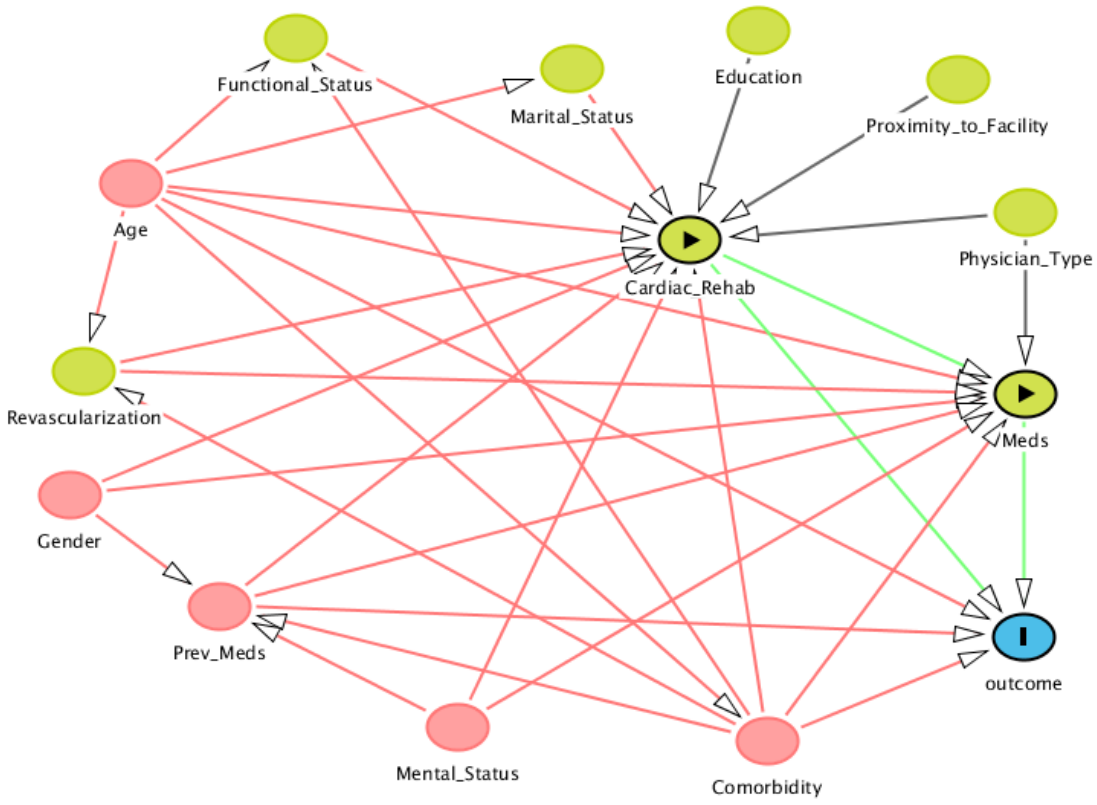
In a recent study of outpatient CR participation in a single hospital-based center in Victoria, Australia, the predictors of attending CR included male gender, having a domestic partner, and close proximity (<30 km) to facility while predictors of not attending included each 1 year increment in age, non-surgical CVD discharge diagnosis, and moderate proximity (30km to 150 km) to facility [25]. In this study, patients participating in at least 3 sessions of a 6-week program or 1 session of a 3-week program defined attendance. Using a subset of hospitals participating in the AHA's Get with the Guidelines Program (GWTG), Brown et al identified dyslipidemia, smoking, admitting diagnosis of STEMI, and use of CABG or PCI procedures during index hospitalization as predictors for referral for CR [26]. In a study of a single center participating in the GWTG program, the authors noted that while ethnicity was not a predictor of referral it was a predictor of enrollment [21]

Qualitative research has identified similar barriers to CR participation. In a recent systematic review of semi-structured interviews and focus groups, Neubeck et al identified provider communication during hospitalization including recommendation or lack of recommendation, timing of CR discussion in relation to surgery, diagnosis or other health information, and inconsistency of advice as system barriers to enrolling in CR programs [27]. The authors also noted that transportation issues, conflicts with work schedule, and language differences as other system barriers to CR participation. On an individual level, the authors reported that patient participation in CR was affected by a patient's understanding and feelings toward the focus of CR sessions (exercise or psychosocial), a patient's understanding of their ability to modify CVD risk factors, and a patient's perceived embarrassment or perceived support and enjoyment from participation.

4.5. Potential Confounders.

The following directed acyclic graph (DAG) was created based upon a review of the literature described previously in this document. According to this diagram, the minimally sufficient adjustment set for estimating the effect of cardiac rehabilitation on outcomes includes age, comorbidity, previous medication, and current medication.

Figure 2.1: Directed Acyclic Graph Describing the Association of Cardiac Rehabilitation to Outcomes



5. Evidence Based Medications

5.1. Introduction.

Secondary prevention guidelines recommend prescribing antiplatelet, beta blockers, ACE inhibitors, and statins at acute MI event discharge to reduce the risk of subsequent events. Each medication has a Class I (useful/effective/beneficial) recommendation for coronary heart disease patients and specific sub-populations as defined in Table 2.1 [11]. Updates to guidelines recommend the use of statins in all post-MI patients removing the LDL-C restrictions on the class I recommendation of statins post-MI [28].

Table 2.1: Secondary Prevention Guideline Medication Recommendations

Medication	Class	LOE	Sub-Population by Condition
Aspirin	I	A	All
Clopidogrel	I	B	Acute coronary syndrome or percutaneous coronary intervention (PCI) with stent placement
B-Blocker	I	A	All
ACE inhibitors	I	A	Left ventricular ejection fraction (LVEF) ≤40%, hypertension, diabetes, or chronic kidney disease
ACE inhibitors	I	B	All other patients
Angiotensin receptor blockers	I	A	Intolerant of ACE inhibitors and have heart failure or have had a MI with LVEF ≤ 40%
Angiotensin receptor blockers	I	B	All other patients intolerant of ACE inhibitors
Statin	I	A	LDL-C is ≥100 mg/dL
Statin	IIa	B	LDL-C is 70 to 100 mg/dL,
LOE=Level of evidence: A – From multiple clinical trials, B – From 1 clinical trial or any number of observational studies Class I – Recommended to perform; Class IIa – Reasonable to perform			

1. Antiplatelet therapy.

Clinical trials have shown that antiplatelet medications are effective at reducing the risk of adverse cardiovascular events by inhibiting the formation of harmful blood clots. In meta-analyses of clinical trials conducted between 1976 and 1986, the Antiplatelet Trialists' Collaboration reported a 25% decrease in the odds of CVD event (MI, stroke, CVD death) and a 30% decrease in the odds of non-fatal MI in those who used antiplatelet therapy compared to those who did not [29]. The Antithrombotic Trialists' Collaboration completed an updated meta-analysis with similar results [30]. In meta-analyses of randomized trials conducted between 2001 and 2006 investigating dual therapy with clopidogrel and aspirin compared to aspirin monotherapy showed a reduction in the risk of the combined outcome of MI, stroke, and death of 12% to 26% [31, 32]. The authors' also note that while antiplatelet therapy is effective in reducing harmful cardiovascular outcomes there is also an increased risk in major bleeding events.

2. Beta adrenergic receptor antagonism (Beta Blocker therapy).

Similar to antiplatelet therapy clinical trial evidence for the effectiveness Beta Blocker (BB) therapy has existed since the 1970's. Research on the biologic pathways where BB therapy has been shown protective against future events is by the drug's effect on heart rate, arterial pressure, and muscle function [33, 34]. An early systematic review of clinical trials, reported a 20% reduction in the odds ratio of death and 24% reduction in the odds ratio of re-infarction in patients randomized to BB therapy compared to control [35]. While use of BB therapy as a class has been shown in clinical trial to reduce post-MI mortality, systematic review and meta-analysis of clinical trials provide inconclusive evidence between different subclasses [36]. Williams et al and DiNicolantonio et al reported that nonselective BB therapy had a greater benefit in reducing

mortality than selective BB therapy while Freemantle et al and Andersen et al did not report any difference in morality between subclasses [34, 37-39].

3. Renin-Angiotensin System Inhibition (ACEi/ARB therapy).

Research has shown that ACE inhibitors are effective in reducing cardiac events in those with and without heart failure. The authors in a meta-analysis of placebo-controlled clinical trials of the use of ACE inhibitors after acute MI initiated between 1990 and 1997 reported a 17% reduction in odds of all-cause mortality and 18% reduction in the odds of cardiovascular mortality in those randomized to ACE inhibitors compared to those randomized to placebo [40]. The trials included in the Domanski meta-analysis mainly included patient with heart failure or left ventricle systolic dysfunction. Three randomized placebo-controlled trials that included patients without heart failure but with atherosclerosis, reported a 14% reduction in odds of all-cause mortality and 18 % reduction in the odds of non-fatal myocardial infarction [41]. Approximately 60% of the patients in this second meta-analysis had an MI prior to study entry. In the analysis of five placebo-controlled trials of ACE inhibitors in patients with heart failure or left ventricle systolic dysfunction, Dagenais et al. also reported a 20% reduction in the odds of non-fatal myocardial infarction. ACE inhibitors, a vasodilator, work on the angiotensin II pathway to affect blood flow and prevent tissue remodeling. ACE inhibitors are used in the treatment of hypertension and also reduce insulin resistance [42]. Aldosterone receptor blockers (ARB) also work on the angiotensin II pathway and have fewer issues with adherence than ACE inhibitors; however, there is not the same level of evidence of ARBs effectiveness in preventing further MI events as with ACE inhibitors [42] . Guidelines recommend use of ARBs in secondary prevention only when ACE inhibitors are not tolerated by patients.

4. Cholesterol lowering via HMG-CoA reductase inhibition (Statin therapy).

Statin therapy reduces the risk of CVD events by limiting the amount of cholesterol in the bloodstream. The authors in a meta-analysis of placebo-controlled trials of elderly patients (≥ 65years old at randomization) with coronary heart disease reported a 22% reduction in the 5 year relative risk for all-cause mortality and a 26% reduction in the 5 year relative risk for non-fatal MI events [43]. In a recently published meta-analysis of randomized trials evaluating statin therapy the results from the placebo-controlled secondary prevention trials showed an 18% reduction in the odds of all-cause mortality and a 31% reduction in the odds of major coronary events [44].

5.2. Evidence of Efficacy of Combination Pharmacotherapy.

Several studies have been conducted investigating the use of guideline recommended medications after acute coronary syndrome (ACS) or acute MI. Two studies from the University of Michigan investigated the effect of combination therapy defined by appropriateness score on 1-year (Mukherjee et al.) and 2-year (Lahoud et al.) mortality in patients recently discharged for acute MI or unstable angina. The appropriateness score categorized the number of medications used at discharge divided by the number of medications recommended by in the AHA/ACA guidelines where a participant did not have a documented contraindication [45, 46]. Level 1 appropriateness specified that a patient used 1 medication where 3 or 4 were recommended while level 4 denoted all recommended medications were used. Besides the differences in the length of follow-up, the Mukherjee study investigated the use of antiplatelet therapy while the Lahoud study specified the investigation of aspirin. Both studies included the use of ACE inhibitors or ARBs, statins, and β Blockers in calculation appropriateness. Regardless of these differences,

both studies reported significantly decreased odds of mortality starting at an appropriateness level of 2 compared to reference Level 0 [46] or reference Level 0 or 1 [45]. Lahoud et al also reported decreased odds of hospitalization for non-fatal CVD events at 2 years at appropriateness level 2 or better in men compared to reference Level 0 or 1. Combination therapy in women did not show an effect on non-fatal CVD events. Nichols et al. compared users of 3 or 4 guideline medications to users of less than 3 medications (referent group) using electronic medical records from Kaiser Permanente, Northwest [47]. These authors' reported a reduction in all-cause mortality, HR (95%CI): 0.84 (0.73 – 0.98), in those who received all guideline medications compared to the reference group. The hazard ratios for any CVD hospitalization and the composite outcome of CVD hospitalization and all-cause mortality were close to 1 and not statistically significant.

Internationally Wong et al investigated the effect of aspirin, beta blockade, statin, and ACEi/ARB on survival among ACS patients admitted to two centers in New Zealand while Danchin et al investigated the use of similar medications on a population of acute MI patients admitted to intensive care units in France [48, 49]. All 1025 participants in the Wong study were using aspirin at hospital discharge. The authors' reported a protective 1 year mortality rate (HR=0.55 [95% CI: 0.30, 1.00]) for those using aspirin, statin, and beta blocker compared to aspirin and beta blocker without regard to use of ACEi/ARB in either group adjusting for continuous GRACE (global registry of acute coronary events) score only. Danchin et al reported a protective 1 year mortality rate (HR=0.43 [95% CI: 0.28, 0.66]) for those initiating triple combination therapy (antiplatelet, beta blocker, and statin) compared to those who did not initiate triple therapy adjusting for the propensity for being prescribed triple combination therapy. Danchin et al reported that hyperlipidemia, admission Killip class 1, PCI during index

hospitalization were positive predictors of triple combination therapy while age, atrial fibrillation, and history of peripheral vascular disease, chronic renal failure, or congestive heart failure were negative predictors of triple combination therapy in their study.

5.3. Medicare Coverage.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 made prescription drug coverage available beginning January 1, 2006 for Medicare beneficiaries who elected to enrolled in the program [50]. Premiums are income based such that low income beneficiaries who are also Medicaid eligible will have very limited out-of-pocket expenses and beneficiaries who have an income over a set poverty criteria will be required to an annual or monthly premium, deductible, and a variable percentage of the actual drug cost [50]. The copayment percentage starts at 25% drops to 0%, coverage gap, then increases to 5% based upon predefined spending limits [50]. While over the counter aspirin is not covered by the Medicare benefit, either generic or brand name options of each of the other medications are covered by Medicare.

5.4. Utilization.

Medication therapy cannot be effective if prescriptions are not filled. In a study of primary non-adherence, not filling first prescription, for cardio-protective medication after acute MI, Jackevicius et al reported that approximately 18% of approximately 12,000 discharge prescriptions for cardiac medication from 4600 eligible patients were not filled within 90 and 120 days after index hospitalization [51]. Restricting results to the four evidence based medication categories, antiplatelet agents (including aspirin) had the most unfilled prescriptions

(44%) while the other three medication had an average of 6% of unfilled scripts within 120 days of index discharge. In a study of Medicare beneficiaries who had an acute MI in 2007, investigators reported that within 1 month of index hospitalization 59%, 51%, 54%, and 46% of beneficiaries filled a prescription for ACEi/ARB, beta blocker, statin, and clopidogrel respectively [52]. Zuckerman et al noted in their sample that prevalence of use declined by less than 7% of beneficiaries for ACEi/ARB, beta blocker, and statin medications over the 33 month follow-up period while a greater decline was observed in clopidogrel prevalence. In a study of patients with coronary artery disease who had a catheterization procedure, the authors reported that of those who were prescribed the medication at discharge 78%, 67%, 47%47%, and 40% of patients self-reported use of aspirin, beta blocker, ACEi, and statin at one year respectively [53].

Reasons for non-adherence to cardiovascular therapy are similar to those of non-initiation of cardiac rehabilitation. Jackevicius et al reported that age, income level, number of prescribed medications prior to index MI, medication counseling during index hospitalization, having a PCI procedure, history of heart failure, and history of MI were related to primary non-adherence to all verse none of the therapies in a patient's post MI evidence based treatment regimen [51]. Investigators from the MAINTAIN study reported that age, less educational attainment, lack of pharmacy benefits, number of discharge medications, lack of medication reminder strategies, being a dialysis patient, and having peripheral vascular disease were all negatively associated with persistence with the evidence based treatment regimen prescribed at discharge [54, 55]. Melloni et al also reported that previous revascularization was positively associated with persistence with the evidence based treatment regimen prescribed at discharge.

6. Utilization of Multiple Guideline Recommendations.

Most of studies of secondary prevention focus on exercise therapy or pharmacotherapy separately, did not include antiplatelet medications in their analysis, or did not comment on use of cardiac rehabilitation [56]. However, Chew et al investigated six month outcomes in patients in the global registry of acute coronary events (GRACE) cohort who were exposed to services and treatment with several in-hospital guideline recommendations including discharge prescriptions and referral to cardiac rehabilitation services [57]. The authors conducted a nested case-control study reporting the proportion of deaths that could be prevented by better-quality utilization of guideline recommendations. Of the medications and services of interest, the attributable fraction associated with increased survival was highest for thienopyridine antiplatelet usage (clopidogrel) (10.9% [95% CI: 2.3, 9.8]) and lowest for beta blockade (0.1% [95% CI: -2.8, 4.8]). The attributable fraction for cardiac rehabilitation referral was also in the top three but had a very wide confidence interval (10.6% [95% CI: -2.4, 21.5]).

CHAPTER 3: METHODS

1. Data

The original research data application to the Chronic Condition Warehouse (CCW) requested claims data for Medicare beneficiaries who were hospitalized in 2008 with a discharge diagnosis in the primary or secondary position of acute myocardial infarction (AMI) defined by International Classification of Diseases, Clinical Modification 9th revision (ICD 9) discharge codes of 410.xx (excluding 410.x2) and were continuously enrolled in Medicare parts A, B, and D from January 1, 2007 to death or December 31, 2009. Starting from this original set of beneficiaries, the initial population defined for this dissertation excluded those who had an MI hospitalization in the year prior to their index event in 2008, had history of substantial frailty (diagnosis of paralysis, Parkinson's disease, or bed sores; or evidence of use of a wheelchair or in-home hospital bed) in the year prior to their index event [58], were less than 65 years old at the time of their index event, or did not survive their index hospitalization. Methods used to further define the study population for each aim are described in subsequent sections of this document. A cohort study using Medicare data is a cost effective method for investigating this study question since elderly patients do not traditionally meet the eligibility requirements for clinical trials.

2. Assessment of Guideline Recommend Therapy

Guideline recommended therapy components had a common definition for all aims. Healthcare Common Procedure Coding System (HCPCS) codes from outpatient and carrier CMS files for Physician services for outpatient cardiac rehabilitation with (93798) or without (93797) continuous ECG monitoring were used to identify cardiac rehabilitation (CR) for this dissertation. Prescription claims from CMS Part D files were linked using National Drug Codes (NDCs) and/or generic names of medications to Anatomical Therapeutic Chemical (ATC) codes to identify medications of interest for this dissertation. Guideline recommend medications (GRM) were identified by ATC codes B01AC for Platelet Aggregation Inhibitors excluding heparin, C10 for HMG CoA Reductase Inhibitors (Statins) and other Lipid Modifying Agents, C09 for Renin-Angiotensin System Inhibitors (ACEi and ARB), C07 for Beta Blockers. Exposure to any Lipid Modifying agent were summarized separately from Statin exposure. Although platelet inhibitors such as aspirin have multiple indications we assumed that utilization at prescription strength in this populations is for secondary prevention of cardiovascular events. Combination GRM use was defined by days' supply remaining for all four GRMs for beneficiaries where revascularization occurred during index period or all GRMs except antiplatelet therapy otherwise.

3. Competing Risk Analysis

In the analysis of survival data, any event that prevents the outcome of interest from occurring is a competing event. Death from any cause is a competing event in analyses of non-fatal outcomes. In aim 1 of this project, the outcomes of interest were the initiation of cardiac rehabilitation and concurrent adoption of multiple guideline recommendations while the outcomes of interest in aim 2 and 3 were disease specific hospitalization and all cause hospitalization after an index MI. An absolute measure of each outcome was computed using cumulative incidence functions (CIF). The CIF, F(t), was computed using a nonparametric competing risks method defining death as the only competing event.

$$\boldsymbol{F(t) = Pr(T \leq t, M = m) = \sum_{t_i \leq t} \left(\frac{d_{mi}}{n_i}\right) \prod_{j=1}^{i-1} \left(1 - \frac{d_j}{n_j}\right)} \quad (1)$$

where events from cause m=1 is the event of interest and m=2 was death from any cause, t_i is a distinct list of event times, d_{mi} is the number of events of interest from cause m that occur at time t_i, n_i is the number of individuals in the risk set just before time t_i, d_j is the number of events of any cause that occur at time t_j, and n_j is the number of individuals in the risk set just before time t_j.

4. Methods Specific to Aim 1

The 12 months before the index hospitalization period was used to define baseline covariates. The index hospital period began with the MI admission and ended when the patient was discharged into the community (loss of inpatient status) based upon the discharge destination codes (Appendix Table 2). If a beneficiary remained an inpatient by being transferred to another medical facility then the index period ended when the beneficiary was discharged into the community after the final continuous transfer. Guideline concordant medical care was assessed from the end of the index hospitalization period until December 31, 2009.

Cohort restriction by post-MI survival time (30, 60, 90, 180, and 366 days) and predicted 1-year mortality <17% (Gagne score <5) defined six subpopulations for analysis in Aim 1. The Gagne comorbidity score has been shown to predict mortality better in elderly populations than other comorbidity measures [59]. Initiation of CR, guideline adoption of combination medication, and guideline adoption of CR and combination medication were outcomes of interest for Aim 1. We estimated the unadjusted cumulative incidence function (CIF) of guideline concordant care within the first year post-MI overall and by survival restricted populations. Study outcomes were used to describe the differences in the CIF computed from competing risk estimators and Kaplan-Meier estimators in the overall population and predicted 1-year mortality population. The CIF computed from the complement of the Kaplan-Meier product limit estimator of the survival distribution function estimates the probability of study outcomes before some time *t* censoring beneficiaries who die before the experiencing the outcome of interest. In this aim, we also described the differences in the CIF between the overall population and each subpopulation. Descriptive statistics (count, proportions, mean, standard deviation) were used to summarize the baseline characteristics of each population.

5. Methods Specific to Aim 2

The 12 months before the index hospitalization period was used to define baseline covariates. The index hospital period began with the MI admission date and ended when the patient was discharged into the community (loss of inpatient status) based upon the discharge destination codes (Appendix Table 2). If a beneficiary remained an inpatient by being transferred to another medical facility then the index period ended when the beneficiary was discharged into the community after the final continuous transfer. The use of outpatient cardiac rehabilitation was assessed in the 60-day exposure window following the index hospitalization period. Outcomes were assessed from the end of the 60-day exposure period until December 31, 2009.

CHAPTER 4: USING TIME-TO-EVENT AND COMPETING RISKS APPROACHES TO ASSESS PATTERNS OF USE OF HEALTHCARE SERVICES AFTER AN INDEX EVENT

1. Introduction.

Healthcare utilization databases are increasingly used to assess quality of care and identify characteristics of patients and providers that may be indicative of sub-optimal treatment and guideline compliance [24, 27, 60]. In the literature, these studies assess how patients are managed after an index event, such as myocardial infarction (MI) [4, 5, 35, 40, 42, 44] or fracture [61, 62]. The results of such studies can be used to shape policy, identify disparities, and design quality improvement activities. Large healthcare utilization databases can be used to identify these index events and then assess whether patients are receiving recommended prescription medications or follow-up healthcare services.

An important methodological consideration in conducting studies of treatment initiation or guideline compliance is how to account for death and loss to follow-up in the study design and analysis. Investigators can restrict the study cohort by requiring patients to survive and not be lost to follow-up for a specific time window. However, selecting patients who survive the window limits generalizability of results when the source population is subject to high mortality and/or the window interval is too long. Dropping patients from the study who die or are censored during follow-up can also lead to selection bias as conditioning on survival or being uncensored can create spurious associations between baseline covariates and the outcome (e.g., guideline compliance). In the analysis, investigators can use Kaplan-Meier estimators to censor

patients who die or treat death as a competing event by using competing risk methods. In a standard Kaplan-Meier time-to-event analysis, patients are followed from a study defined start time until an event of interest occurs or until they are censored. Assuming non-informative censoring, this approach results in an estimate of the percentage of patients who had an event of interest at a point in time as if the risk of censoring could be removed. When patients are censored because of death, this target estimation is sub-optimal since the risk of death cannot be removed. Alternatively, competing risk models can be used to estimate the percentage of patients who would initiate treatment before death.

In the present paper, we use time to adoption of guideline recommendations for secondary prevention in heart disease patients from the American Heart Association (AHA) as an empirical example to investigate the implication of implementing these different methods to account for death in post-MI Medicare beneficiaries [63]. We first examined how increasing survival requirements affected the characteristics of the study cohort. We then compared the Kaplan-Meier estimates of the percentage of patients receiving recommended treatments to estimates from competing risk approaches. The goal of this study was to illustrate how employing competing risk analysis is preferable to survival restriction and censoring at death in the analysis of health care utilization after an anchoring event. This study also illustrates how guideline recommendations are being utilized in a large elderly population. While use of these guideline components have been described separately less is known about concurrent use of recommendations.

2. Methods.

2.1. Data/Study Population

We used data from the Centers for Medicare and Medicaid Services (CMS) to investigate prescription fills of guideline recommended medications (GRMs) and use of outpatient cardiac rehabilitation services after myocardial infarction (MI). Medicare beneficiaries who were hospitalized in 2008 for MI defined by discharge code 410.xx (excluding .x2) in first or second position, were 65 to 95 years old at the time of their index and were continuously enrolled in Medicare Part A, B, and D between January 2007 and death or end of 2009 were included in our study. Beneficiaries were included in this study if they survived their index hospitalizations and had a community based discharge destination code (Appendix Table 2). Beneficiaries were excluded from this study if they had an MI hospitalization in the year prior to their index event in 2008 or had evidence of substantial frailty (diagnosis of paralysis, Parkinson's disease, or bed sores; or evidence of use of a wheelchair or in-home hospital bed) in the year prior to their index event [58].

2.2. Study Design

The 12 months before the index hospitalization period was used to define baseline covariates (Figure 4.1). The index hospital period began with the admission date of the first MI hospitalization in 2008 and ended when the patient was discharged into the community (loss of inpatient status) based upon the discharge destination codes (Appendix Table 2). If a beneficiary remained an inpatient by being transferred to another medical facility then the index period ended when the beneficiary was discharged into the community after the final continuous transfer. Guideline concordant medical care was assessed from the end of the index hospitalization period until December 31, 2009.

2.3. Variable Definitions

Demographic characteristics (e.g., age, gender, and racial status) were obtained from the CMS enrollment file. Comorbidities and procedures were identified using the Medicare Standard Analytic Files using International Classification of Diseases Ninth (ICD 9) Revision codes, Current Procedural Terminology (CPT) codes, and Healthcare Common Procedure Coding System (HCPC) codes. We identified relevant baseline and index period characteristics such as history of hypertension, hyperlipidemia, revascularization, and length of stay. The Gagne comorbidity score, which predicts mortality better in elderly populations than other comorbidity measures, was computed from the baseline characteristics [59]. Frailty was quantified by computing the probability of diminished activities of daily living using model coefficients [58].

2.4. Outcome Definitions

Therapies of interest in our study were initiation of outpatient CR defined by records with CPT codes 93797 and 93798 and concordant use of GRMs identified in Part D records. Guidelines recommend prescriptions for antiplatelet medication, renin-angiotensin system inhibitors, beta adrenergic receptor antagonism, and HMG CoA reductase inhibitors (statins) for MI survivors. Aspirin is also recommended however, it is not reliably captured in Part D records because of it's over the counter availability. Concordant use of GRMs was defined as the first day after index period that a beneficiaries had any days' supply remaining for a combination of all four GRMs for beneficiaries where revascularization occurred during index period or all GRMs except antiplatelet therapy otherwise. We also identified guideline concurrent care (GCC) as the first date when beneficiaries were using both GRMs and CR services. In the definition of concurrent use of CR and GRMs, a beneficiary was assumed a user of CR indefinitely after CR initiation while prescription fill dates and days' supply of medication defined combination GRM discontinuation. If a beneficiary discontinued combination GRM use before CR initiation then they would not be considered a concurrent user until they started using the appropriate level of combination GRMs again.

2.5. Cohort Restrictions

We explored the effect of requiring survival for varying lengths of time on the post-MI use of GRMs and/or CR services. We considered five different post-MI discharge survival restrictions: 30, 60, 90, 180, and 366 days. The 30, 60, and 90-day time intervals were based the common lengths of days' supply for GRMs. The 180-day and 1-year time points were chosen to represent extreme scenarios [64]. We also created a cohort restricted by Gagne comorbidity score [59]. Gagne et al defined high risk of 1-year mortality as ≥ 17%. We defined the final restricted population as beneficiaries with a comorbidity score <5 to define a population with a lower risk of 1-year mortality.

2.6. Statistical Analysis

Descriptive statistics (count, proportions, mean, standard deviation) were used to summarize the characteristics of each population. Standardized differences between the overall population and each restricted population were computed. Kaplan-Meier estimates were used to compute the risk of death post-MI. Two methods were used to estimate the cumulative incidence function (CIF) of guideline concordant care. First, CIF estimates were computed from the complement of the Kaplan-Meier (KM) product limit estimator of the survival distribution function, 1-S(t) in which individuals were censored by both death and end-of-study. Let T be the time from discharge to the event of interest (i.e. CR initiation) or censoring. Under those conditions, the complement of the Kaplan-Meier estimator estimates the probability of CR initiation before some time t, CIF(t) = Pr(T<t), assuming all censoring events are independent of CR initiation. The larger the proportion of the population that dies before CR initiation, the higher the degree to

which the independence assumption is violated since death prevents the event of interest from occurring.

For the competing risk approach, let *T* be the time from discharge to censoring, death, or use of guideline recommended health care whichever comes first and let *J* be an indicator variable that specifies the type of event. Let *J* have a value of 1 when *T* refers to prevention method (i.e. CR initiation), 2 when referring to death before prevention method, and 0 when referring to censoring occurring before an event of either type. The competing risk method estimates the joint probability of a specific event occurring before a given time point, $CIF(t) = Pr(T<t , J=j)$ which can be interpreted as the probability of CR initiation before death at time *t* when J=1. In the competing risk approach, the population at risk at each event time excludes individuals who have had any event before time *t* [65]. This method allows investigators to estimate the CIF for the event of interest (initiation of CR) and any competing event (death) separately. The estimator assumes that each cause specific event type is independent of each other [66]. SAS uses a nonparametric estimator to calculate cumulative incidence, CIF(t) = Σ(number of deaths at time *t* from cause j/ number at risk at *t*) *(KM estimate of survival at time *t-1*) [67]. To describe the difference between these approaches, note that for the KM approach $CIF_{KM}(t) = 1 – S_{KM}(t)$ and for the competing risk approach $CIF_{j=1}(t) + CIF_{j=2}(t) = 1 – S_J(t)$. All analyses were done using SAS 9.4 or greater.

3. Results.

We identified 78,479 beneficiaries who met study criteria and who averaged 405 days of follow-up time. The overall population had an average age 78 years old and 56% of beneficiaries were female (Table 4.1). The most common comorbid conditions in the study population were hypertension (84%), hyperlipidemia (66%), congestive heart failure (46%), and diabetes, (41%). As we restricted the study cohort by increasing amounts of post-MI survival time, the number of beneficiaries in each population decreased, however, there were very few differences in the distribution of measured baseline characteristics (Table 4.1). Differences in the measured covariates occurred in the 366-day restricted population which had greater than 10% standardized differences from the overall population for revascularization during index period, probability of diminished daily activities (frailty proxy), and Gagne score that were (data not shown). The proportion of beneficiaries with an index period revascularization procedure increased while the mean frailty probability and comorbidity score decreased with increasing restriction on survival time for population inclusion. In addition, the proportion of beneficiaries at least 85 years old at the time of their index MI decreased with increasing restriction on survival time so each restricted population is slightly younger than the overall population. The survival rate in the overall population was lower than in the survivor-restricted populations (Figure 4.2). The proportion of those who died in the overall population was 4.5% at 30 days post-MI increasing to 17% at 1-year post-MI. The proportion of those who died at 1 year was 13.1%, 11.0%, and 9.3% in 30-day survivor, 60-day survivor, and 90-day survivor populations respectively. The survival-restricted population survival curves were similar in shape to the overall population survival curve with a shift to the right for each additional increment in required survival time for inclusion in the population.

Estimates of guideline adoption increased with increasing amounts of survival restriction (Table 4.2). Differences in the cumulative incidence between each subsequent survivor-restricted population were small. When the survival requirement for population inclusion was 90 days or less, the confidence intervals for the cumulative incidence of treatment for each survivor restricted population overlapped. However, confidence intervals for the cumulative incidence of treatment did not overlap when at least 180 days of survival were required for population inclusion. The difference in cumulative incidence estimates between the unrestricted population and each survivor-restricted population was larger at 1-year post-discharge than at 30 days post-discharge. Cumulative incidence of treatment adoption for the predicted lower mortality population was similar to the 1-year survivor restricted population for each study treatment. We observed that the Kaplan-Meier (KM) estimates of the incidence of CR initiation overestimated the competing risk method estimates. The magnitude of the difference in estimates between methods increased with an increase in time since discharge (Table 4.2). At 30 days post-MI, the difference in CR initiation between KM estimate and the competing risk estimate was only 0.2. However, at 1-year post-MI, the difference between estimation methods was 0.9. Although the estimates for CR initiation were higher in the comorbidity score restricted population than the unrestricted population, the difference between estimates was similar, 0.2 and 0.7 at 30 days and 1-year post-MI respectively. The incidence of CR initiation was low regardless of the estimation method used ranging from 6.7% at day 30 to 17% at 1 year post-discharge depending on the estimation method and population analyzed (Table 4.2).

Similar to the cumulative incidence for initiating CR, the KM estimates for post-MI GRM use and guideline concurrent care were higher than the competing risk estimates (Table 4.2). Approximately, 30% of the each population already had prescription fills for the concordant

number of GRMs at MI discharge. At 30 days post discharge, the competing risk method estimated 42.6% (95%CI: 42.2%, 42.9%) of the overall population with concordant GRM use while the KM method estimated 42.8% (95%CI: 42.5%, 43.1%) with concordant GRM use. At 1-year post discharge, the proportion of beneficiaries with concordant GRM use rose to 51.4% (95%CI: 51.0%, 51.7%) using competing risk estimator and 52.9% (95%CI: 52.5%, 53.2%) using the KM estimator. Less than 10% of any of the populations were concurrently compliant with both CR and combination GRMs within 1 year of MI discharge.

Cumulative incidence curves produced using the competing risk estimator for each study treatment and the respective competing event of death are presented in Figure 4.3. CR initiation and guideline concurrent care curves start to peak at approximately 90 days post discharge then remain relatively constant after 180 days. The cumulative incidence for post-MI GRM use, however, increases rapidly before 90 days post discharge and continues to increase after 90 days but at a slower rate than before 90 days. The magnitude of the cumulative incidence of death before CR initiation was similar to the magnitude of the cumulative incidence of CR initiation. The magnitude of death before GRM use was lower than the magnitude of death before CR initiation. At 1-year post discharge, 17% and 11% died before initiation CR and concordant use of GRMs respectively.

4. Discussion.

In a population-based study of patients discharged alive after MI, we compared different approaches to estimating the percentage of patients receiving guideline-recommended medications or initiating cardiac rehabilitation after hospital discharge. Restricting the study cohort by survival reduced the population at risk and appeared to select for more guideline obedient patients, as restriction increased the estimated number of patients who would initiate CR and GRM during follow-up. Censoring patients who die is an alternative approach to requiring survival; however, implicitly censoring by death assumes that patients who die could still go on to initiate therapy. The solution to the problems presented in the paper is to use competing risk analysis with or without further restriction by comorbidity score. In our study, we saw relatively modest differences between the Kaplan-Meier estimates of the cumulative probability of initiation of CR and GRM and the competing risk estimates. In studies subject to stronger mortality, these differences would be larger.

Our estimates of CR initiation were similar to other studies where the differences in results are likely a result of differences in the populations studied or analysis methods. A previous study of Medicare beneficiaries at least 65 years old who survived at least 30 days post discharge and had a length of stay of 30 days or less reported 13.9% of MI patients initiated CR within 1 year [20]. A more recent study of patients at least 65 years old at MI hospitalization admitted to hospitals volunteering to participate in a national MI registry reported that 20.4% of MI patients (32.6% of referred patients) initiated CR within 1-year post-MI [68]. Doll et al, required survival 1-week post discharge but also restricted their population by prescriptions for GRMs [68]. Both of these studies reported the observed proportion of CR initiators from their initial cohorts without accounting for the competing event of death, therefore, these estimates would be higher

than estimates in similar populations from the current study. Promoting the use of CR programs remains an opportunity for public health intervention given that less than half of any population studied participated in at least 1 session with in the first year post-MI discharge.

Beneficiaries were more likely to fill prescriptions for concordant guideline medications than participate in cardiac rehabilitation in this study. Concordant GRM use from this study was more similar to a study of acute coronary syndrome (ACS) patients with commercial health plans (37.5% at 6 months) than to registry study of commercially insured patients with cardiovascular disease (56% at 6 months) [64, 69]. Although more beneficiaries filled prescriptions for GRMs than initiated CR, the change in the proportion of participation from 30 days to 1-year post-MI was the similar for both CR and concordant GRMs in populations where 6 months or less of survival was required for inclusion. Approximately one-half of those who initiated CR within the first year post-MI were also concurrently using 3-4 GRMs.

Results from our analysis have implications for outcome studies using guideline treatments as an exposure. Beneficiaries experienced long delays between discharge and CR initiation. The proportion of CR initiators nearly doubled between 30 days and 90 days post discharge. The mean time to CR initiation of 56 days in this study was similar to what has previously been reported [17]. However, the distribution of time to initiation among initiators was skewed right (median 33 days); so, if we restricted our population using the mean time to initiation as the criterion for inclusion then more than half of those who would eventually initiate treatment would be included in the restricted population. Assuming 75% of eventual CR initiators do so within a 60 day exposure widow and it takes 180 days for 95% of eventual CR initiators to start, methods presented by Austin et al suggest an outcome hazard ratio of 0.73 when the true outcome hazard ratio was 0.75 using Monte Carlo simulations [70]. Survival bias in this case is

overestimating the protective effect of treatment but not by very much. Studies that aim to assess the effects of CR should consider the above factors when designing outcome studies with fixed exposure windows.

Restriction has been used in the study of the effect of protective treatments on mortality and morbidity outcomes to reduce biases associated with conducting these studies using observational data [71-73]. Cohorts restricted by baseline characteristics such as comorbidity score may introduce some selection bias but they may reduce confounding by indication. We demonstrated that treatment adoption by comorbidity-restricted population was similar to the 1-year survival restricted population. We would recommend that investigators restrict cohorts by baseline prediction of survival than actual survival in the extreme case of 1-year survival for cohort eligibility.

Our large sample size was a strength of our study. It permitted us to apply several types of restrictions and maintain sufficient numbers of beneficiaries in each subpopulation to stably estimate adoption of guideline recommendations. Women, a subgroup that is often under-represented in CR trials, comprised approximately half of each population [4]. Because we used both outpatient and pharmacy claims data for this study, we were able to avoid recall bias in the definition of treatment assignments. However, we may have underestimated GRM use due to over-the-counter aspirin use and some beneficiaries initiating treatment on samples or low-cost generic medications that were not recorded in the pharmacy claims [74, 75]. Unlike GRM use, CR services should be reliably captured in the outpatient claims data since providers would not be reimbursed without submitting a claim. Unlike GRM use, CR services should be reliably captured in the outpatient claims data since providers would not be reimbursed without submitting a claim.

In conclusion, we discussed different approaches to accounting for death applied to a study of the use of guideline-recommended therapies after MI. We found that restricting the population, as is commonly done, resulted in somewhat higher estimates of CR and GRM use. We saw relatively modest differences between the Kaplan-Meier estimates and the competing risk estimates. In studies where mortality is more common, restricting the study to patients who survive may affect generalizability and may introduce some survivor bias in the results. In these settings, competing risk approaches would be preferable.

5. Tables

Table 4.1: Characteristics of Study Populations

Characteristics	Overall	030 Day Survivors	060 Day Survivors	090 Day Survivors	180 Day Survivors	366 Day Survivors	Comorbidity Score
Overall	78,479	74,948 (95.5%)	73,187 (93.3%)	71,815 (91.5%)	68,737 (87.6%)	63,770 (81.3%)	64,317 (82.0%)
Demographics							
Age							
Mean (SD)	77.9 (7.57)	77.7 (7.51)	77.6 (7.48)	77.6 (7.46)	77.5 (7.42)	77.3 (7.36)	77.7 (7.56)
Gender							
Female	43,947 (56.0%)	41,930 (55.9%)	40,914 (55.9%)	40,135 (55.9%)	38,403 (55.9%)	35,523 (55.7%)	35,901 (55.8%)
Minority							
Yes	10,641 (13.6%)	10,175 (13.6%)	9,916 (13.5%)	9,725 (13.5%)	9,297 (13.5%)	8,574 (13.4%)	8,062 (12.5%)
Index Hospitalizations							
Revascularization							
Angioplasty	28,639 (36.5%)	28,185 (37.6%)	27,924 (38.2%)	27,703 (38.6%)	27,113 (39.4%)	26,050 (40.8%)	25,890 (40.3%)
CABG	6,970 (8.9%)	6,892 (9.2%)	6,853 (9.4%)	6,819 (9.5%)	6,727 (9.8%)	6,444 (10.1%)	6,237 (9.7%)
Any ICU Stay	43,304 (55.2%)	41,417 (55.3%)	40,488 (55.3%)	39,742 (55.3%)	38,095 (55.4%)	35,365 (55.5%)	35,365 (55.0%)
Any CCU Stay	29,774 (37.9%)	28,658 (38.2%)	28,115 (38.4%)	27,659 (38.5%)	26,629 (38.7%)	24,934 (39.1%)	24,898 (38.7%)
Discharge Home							
No Hospital Transfers	59,300 (75.6%)	56,603 (75.5%)	55,338 (75.6%)	54,356 (75.7%)	52,152 (75.9%)	49,134 (77.0%)	49,270 (76.6%)
Baseline Medications							
Baseline Doughnut Hole Gap	26,455 (33.7%)	25,052 (33.4%)	24,349 (33.3%)	23,784 (33.1%)	22,536 (32.8%)	20,453 (32.1%)	19,323 (30.0%)

Characteristics	Overall	030 Day Survivors	060 Day Survivors	090 Day Survivors	180 Day Survivors	366 Day Survivors	Comorbidity Score
Baseline Comorbidities							
Proxy Frailty Mean (SD)	6.4 (6.47)	6.2 (6.21)	6.1 (6.08)	6.1 (5.99)	6.0 (5.84)	5.8 (5.58)	5.7 (5.23)
Comorbidity Score Mean (SD)	2.4 (2.49)	2.3 (2.44)	2.3 (2.42)	2.2 (2.39)	2.1 (2.35)	2.0 (2.30)	1.5 (1.58)
Conditions							
Hypertension	65,653 (83.7%)	62,829 (83.8%)	61,401 (83.9%)	60,296 (84.0%)	57,765 (84.0%)	53,572 (84.0%)	53,935 (83.9%)
Hyperlipidemia	51,936 (66.2%)	50,136 (66.9%)	49,188 (67.2%)	48,407 (67.4%)	46,645 (67.9%)	43,709 (68.5%)	43,114 (67.0%)
Congestive Heart Failure	36,153 (46.1%)	33,796 (45.1%)	32,602 (44.5%)	31,647 (44.1%)	29,505 (42.9%)	26,332 (41.3%)	23,875 (37.1%)
Uncomplicated Diabetes	32,260 (41.1%)	30,798 (41.1%)	30,071 (41.1%)	29,438 (41.0%)	28,012 (40.8%)	25,723 (40.3%)	24,389 (37.9%)
Cardiac Arrhythmia	29,533 (37.6%)	27,884 (37.2%)	27,061 (37.0%)	26,397 (36.8%)	24,984 (36.3%)	22,762 (35.7%)	21,035 (32.7%)
Chronic Pulmonary Disease	26,868 (34.2%)	25,375 (33.9%)	24,557 (33.6%)	23,945 (33.3%)	22,546 (32.8%)	20,376 (32.0%)	18,437 (28.7%)
Electrolyte Disorders	22,731 (29.0%)	21,157 (28.2%)	20,377 (27.8%)	19,783 (27.5%)	18,547 (27.0%)	16,709 (26.2%)	13,791 (21.4%)
Deficiency Anemia	22,213 (28.3%)	20,879 (27.9%)	20,162 (27.5%)	19,562 (27.2%)	18,330 (26.7%)	16,449 (25.8%)	13,171 (20.5%)
Osteoporosis or Osteoarthritis	21,576 (27.5%)	20,665 (27.6%)	20,194 (27.6%)	19,802 (27.6%)	18,995 (27.6%)	17,639 (27.7%)	17,360 (27.0%)
Peripheral Vascular Disease	18,058 (23.0%)	17,090 (22.8%)	16,585 (22.7%)	16,141 (22.5%)	15,235 (22.2%)	13,823 (21.7%)	11,759 (18.3%)
Cancer	9,919 (12.6%)	9,157 (12.2%)	8,774 (12.0%)	8,492 (11.8%)	7,856 (11.4%)	7,050 (11.1%)	5,901 (9.2%)
Cerebrovascular Disease	9,505 (12.1%)	8,932 (11.9%)	8,666 (11.8%)	8,431 (11.7%)	7,960 (11.6%)	7,186 (11.3%)	6,516 (10.1%)
Renal Disease	4,890 (6.2%)	4,496 (6.0%)	4,320 (5.9%)	4,136 (5.8%)	3,763 (5.5%)	3,268 (5.1%)	1,038 (1.6%)
Rheumatic Disease	3,837 (4.9%)	3,685 (4.9%)	3,617 (4.9%)	3,543 (4.9%)	3,399 (4.9%)	3,134 (4.9%)	3,097 (4.8%)

Note: Cells highlighted in yellow have a standardized difference between the restricted population and the overall population that is greater than 10%.

Table 4.2: Post-MI Cumulative Incidence Estimates of Cardiac Rehabilitation Initiation, Concordant GRM, and Guideline Concurrent Care by Restriction and Calculation Method at Selected Time Points

Analysis Type	Restriction Method	Days Since Discharge 30	60	90	180	366
Cardiac Rehabilitation						
Competing Risk	None	6.7 (6.5, 6.8)	10.9 (10.6, 11.1)	12.4 (12.2, 12.6)	13.7 (13.4, 13.9)	14.2 (14.0, 14.5)
Kaplan-Meier	None	6.9 (6.7, 7.0)	11.3 (11.1, 11.5)	13.0 (12.8, 13.3)	14.4 (14.2, 14.7)	15.1 (14.8, 15.3)
	030 Day Survivors	7.0 (6.8, 7.2)	11.4 (11.2, 11.6)	13.1 (12.9, 13.3)	14.5 (14.3, 14.8)	15.2 (14.9, 15.4)
	060 Day Survivors	7.1 (6.9, 7.3)	11.6 (11.4, 11.8)	13.3 (13.1, 13.5)	14.7 (14.4, 15.0)	15.3 (15.1, 15.6)
	090 Day Survivors	7.2 (7.0, 7.4)	11.8 (11.6, 12.0)	13.5 (13.3, 13.8)	14.9 (14.6, 15.2)	15.6 (15.3, 15.8)
	180 Day Survivors	7.5 (7.3, 7.7)	12.2 (12.0, 12.5)	14.0 (13.7, 14.2)	15.4 (15.2, 15.7)	16.1 (15.8, 16.3)
	366 Day Survivors	7.9 (7.7, 8.1)	12.8 (12.6, 13.1)	14.7 (14.4, 15.0)	16.2 (15.9, 16.5)	16.8 (16.5, 17.1)
	Predicted 1-yr Survivors	7.9 (7.7, 8.1)	12.9 (12.7, 13.2)	14.8 (14.5, 15.1)	16.3 (16.0, 16.6)	17.0 (16.7, 17.3)
Competing Risk	Predicted 1-yr Survivors	7.7 (7.5, 7.9)	12.5 (12.3, 12.8)	14.3 (14.0, 14.6)	15.7 (15.4, 16.0)	16.3 (16.0, 16.6)
Guideline Recommend Medication (GRM)						
Competing Risk	None	42.6 (42.2, 42.9)	45.1 (44.8, 45.5)	46.5 (46.2, 46.9)	48.9 (48.6, 49.3)	51.4 (51.0, 51.7)
Kaplan-Meier	None	42.8 (42.5, 43.1)	45.6 (45.2, 45.9)	47.1 (46.8, 47.5)	49.8 (49.5, 50.2)	52.9 (52.5, 53.2)
	030 Day Survivors	43.5 (43.1, 43.8)	46.2 (45.9, 46.6)	47.8 (47.4, 48.1)	50.5 (50.1, 50.8)	53.4 (53.1, 53.8)
	060 Day Survivors	43.8 (43.4, 44.1)	46.5 (46.2, 46.9)	48.1 (47.7, 48.4)	50.7 (50.4, 51.1)	53.7 (53.3, 54.0)
	090 Day Survivors	44.0 (43.6, 44.3)	46.7 (46.4, 47.1)	48.3 (47.9, 48.6)	50.9 (50.6, 51.3)	53.9 (53.5, 54.2)
	180 Day Survivors	44.4 (44.0, 44.7)	47.1 (46.8, 47.5)	48.7 (48.3, 49.1)	51.3 (51.0, 51.7)	54.2 (53.9, 54.6)
	366 Day Survivors	44.9 (44.5, 45.3)	47.7 (47.3, 48.1)	49.2 (48.8, 49.6)	51.9 (51.5, 52.3)	54.8 (54.4, 55.2)
	Predicted 1-yr Survivors	44.7 (44.3, 45.1)	47.5 (47.1, 47.9)	49.1 (48.7, 49.5)	51.7 (51.3, 52.1)	54.6 (54.2, 55.0)
Competing Risk	Predicted 1-yr Survivors	44.5 (44.1, 44.9)	47.2 (46.8, 47.6)	48.6 (48.2, 49.0)	51.0 (50.6, 51.4)	53.5 (53.2, 53.9)

Analysis Type	Restriction Method	Days Since Discharge 30	60	90	180	366
Guideline Concurrent Care						
Competing Risk	None	3.3 (3.2, 3.4)	5.1 (5.0, 5.3)	5.9 (5.8, 6.1)	6.9 (6.7, 7.0)	7.6 (7.4, 7.8)
Kaplan-Meier	None	3.4 (3.3, 3.5)	5.3 (5.2, 5.5)	6.2 (6.0, 6.4)	7.3 (7.1, 7.4)	8.1 (7.9, 8.3)
	030 Day Survivors	3.4 (3.3, 3.6)	5.4 (5.2, 5.6)	6.2 (6.1, 6.4)	7.3 (7.1, 7.5)	8.1 (7.9, 8.3)
	060 Day Survivors	3.5 (3.4, 3.6)	5.5 (5.3, 5.7)	6.3 (6.2, 6.5)	7.4 (7.2, 7.6)	8.2 (8.0, 8.4)
	090 Day Survivors	3.6 (3.4, 3.7)	5.6 (5.4, 5.8)	6.4 (6.3, 6.6)	7.5 (7.3, 7.7)	8.3 (8.1, 8.5)
	180 Day Survivors	3.7 (3.6, 3.8)	5.8 (5.6, 6.0)	6.7 (6.5, 6.9)	7.7 (7.5, 7.9)	8.6 (8.4, 8.8)
	366 Day Survivors	3.9 (3.7, 4.0)	6.1 (5.9, 6.3)	7.0 (6.8, 7.2)	8.1 (7.9, 8.4)	9.0 (8.8, 9.2)
	Predicted 1-yr Survivors	4.0 (3.8, 4.1)	6.2 (6.0, 6.4)	7.1 (6.9, 7.3)	8.3 (8.1, 8.5)	9.2 (9.0, 9.4)
Competing Risk	Predicted 1-yr Survivors	3.9 (3.7, 4.0)	6.0 (5.8, 6.2)	6.9 (6.7, 7.1)	8.0 (7.8, 8.2)	8.8 (8.6, 9.0)

6. Figures

Figure 4.1: Study Design

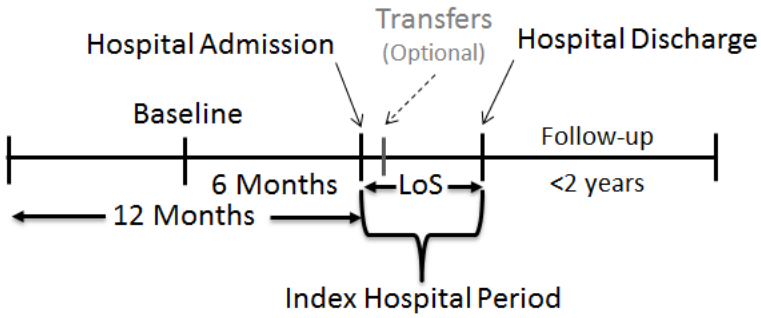


Figure 4.2: Study Population 1 Year Survival Curve

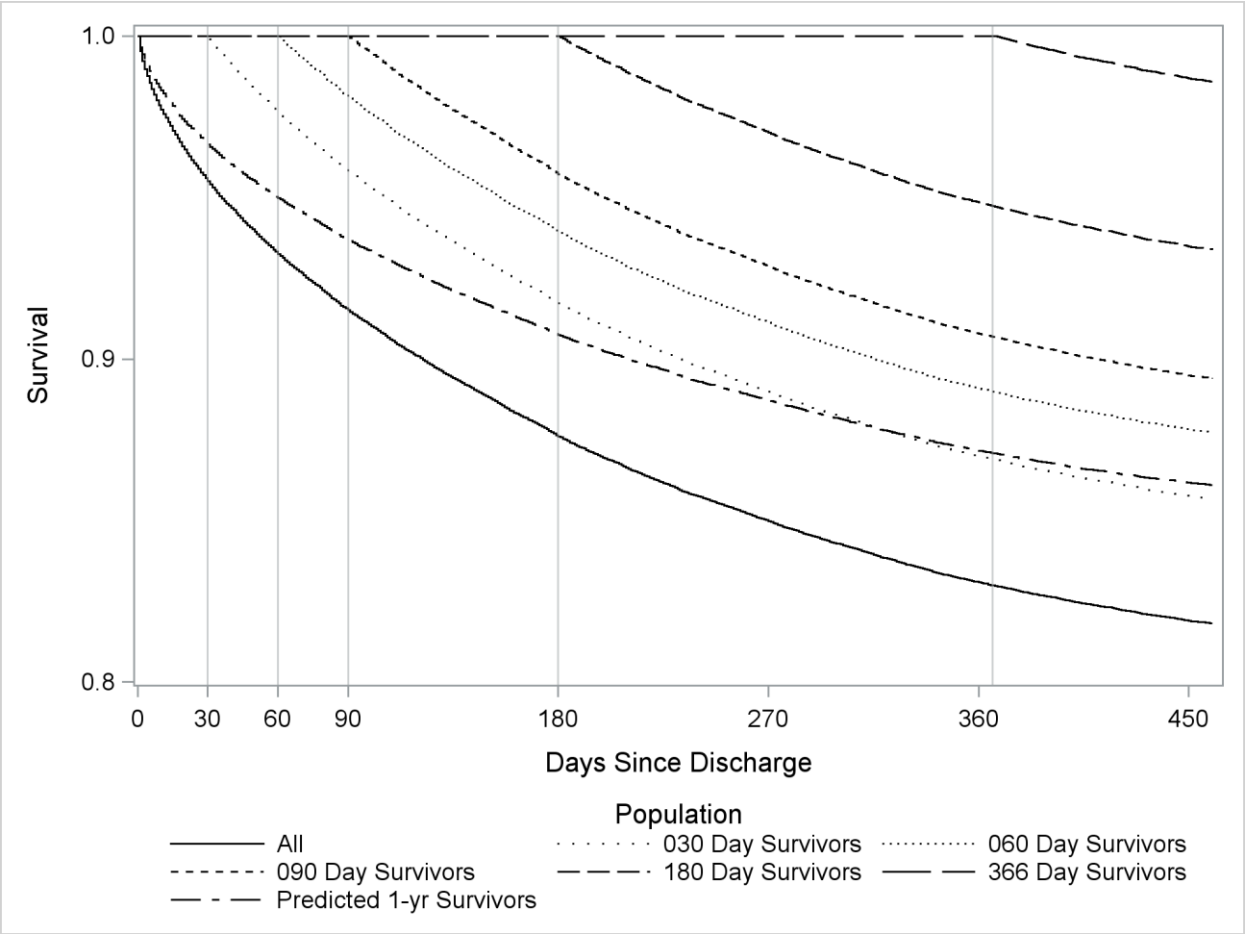
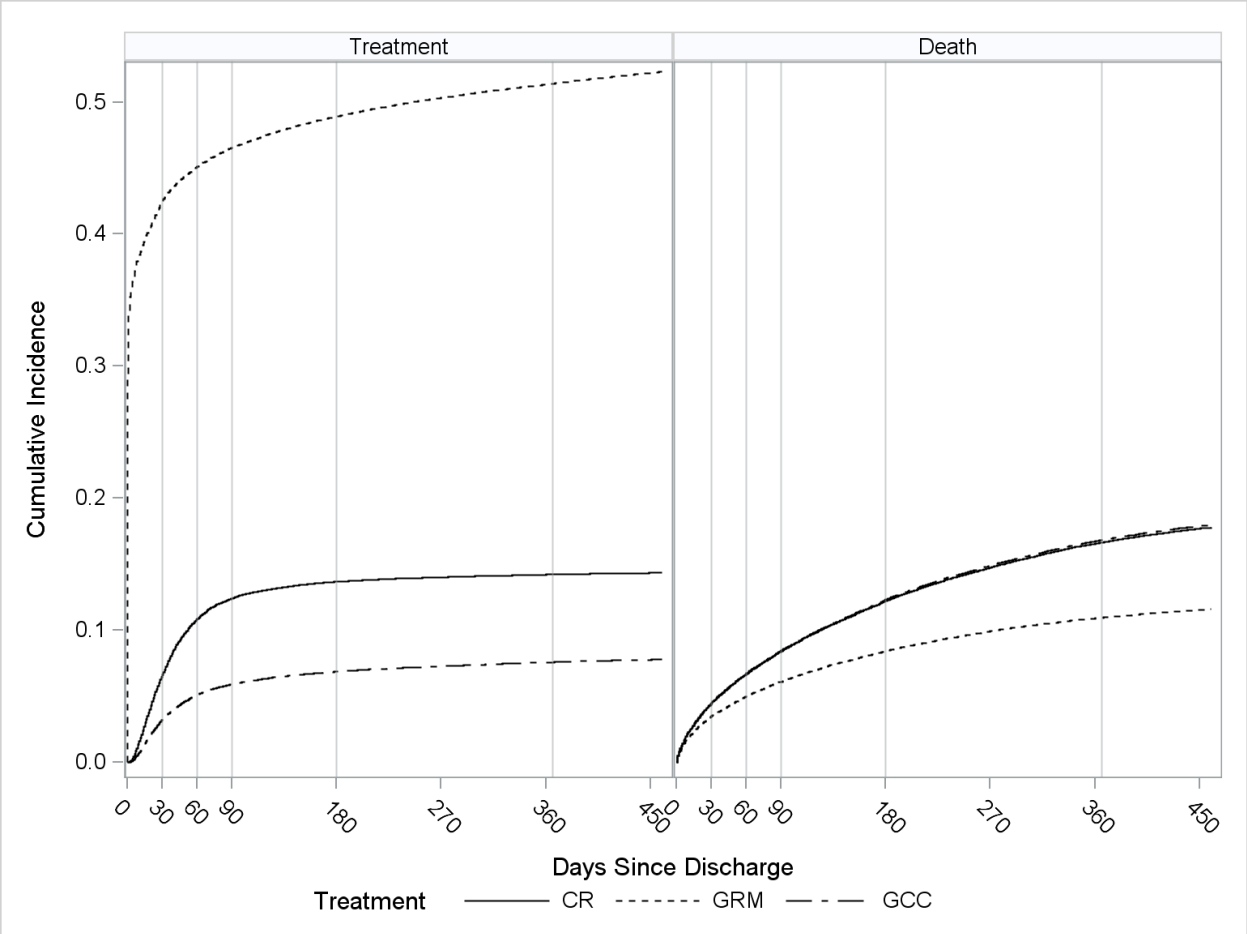


Figure 4.3: Competing Risks Estimates of Cumulative Incidence of Cardiac Rehabilitation (CR) Initiation, Concordant Guideline Recommended Medication (GRM) Use, and Guideline Concurrent Care (GCC) After MI



CHAPTER 5: EFFECT OF INITIATING CARDIAC REHABILITATION AFTER MYOCARDIAL INFARCTION ON SUBSEQUENT HOSPITALIZATIONS IN OLDER ADULTS

1. Introduction.

History of myocardial infarction is prevalent in 7.6 million people over the age of 20 in the US based upon a recent national survey with approximately 85% occurring in adults ≥ 60 years old [76]. Patients with a history of MI have a higher risk of a recurrent MI or other cardiovascular disease (e.g. heart failure, stroke) than the overall population [76]. Recurrent MI or cardiovascular related death was estimated to occur in 17% of men and 21% of women ≥ 45 years old within five years of their initial MI [76]. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for secondary prevention of cardiovascular events and management of patients with acute coronary syndromes recommend use of evidence-based medications and participation in outpatient cardiac rehabilitation programs for MI survivors to reduce the high risk of these future events [63].

Cardiac rehabilitation (CR) programs showed a protective effect on mortality similar to pharmacotherapy when compared to usual care in meta-analyses of randomized control trials comprising patients hospitalized with a myocardial infarction or acute coronary syndrome [4, 5]. While the clinical trials in these meta-analyses focused on mortality benefits, few investigators reported the benefits of CR on specific cardiovascular or all-cause hospitalization after an MI. Meta-analysis of studies of the association of CR and subsequent hospitalization after an index event were heterogeneous so the evidence for the benefits of CR on these outcomes is not as strong as the evidence for mortality benefit [16, 77]. Since CR clinical trials enrolled younger

mostly white male participants, there exists an opportunity to understand the efficacy of these programs in older more gender diverse populations than has previously been studied. Additionally, because many of the clinical trials investigating CR were completed several decades ago, there is some debate if CR programs still provide a benefit in the modern medical environment [77, 78]. Given the large proportion of the population that is effected by recurrent cardiovascular events and the strength of evidence on the efficacy of CR programs in older adults with a history of MI, it is essential to investigate the routine and optimal use of secondary prevention methods in this population.

The goal of this study was to investigate the effect of initiating outpatient cardiac rehabilitation within 60 days post-MI on cardiac related and all-cause hospitalizations in a modern medical environment. For each type of hospital admission outcome, the 1-year risk difference between the CR initiators and non-initiators was computed among Medicare beneficiaries. Since CR services are underutilized in practice, we also performed stratified analyses by age, comorbidity score, and secondary prevention medication use to explore subpopulations that can be targeted future intervention efforts to improve participation in CR programs [20, 79].

2. Methods

2.1. Study Population

All Medicare beneficiaries between 65 and 88 years old who were hospitalized between January 1, 2008 and December 31,2008 for acute MI, had a revascularization procedure during the index hospitalization period, and were continuously enrolled in Medicare Part A, B, and D between January 2007 and death or December 2009 were eligible for this study. We defined

acute MI hospitalization by International Classification of Diseases, Clinical Modification 9th revision (ICD 9) diagnostic code 410.xx (excluding 410.x2) in the first or second discharge position of hospital summary data from Medicare Provider Analysis and Review (MedPAR) files. Revascularization was identified from ICD 9 procedure codes, Healthcare Common Procedure Coding System (HCPCS) codes, and Current Procedural Terminology (CPT) codes (Appendix Table 4). Beneficiaries were excluded from this study if they had an MI hospitalization in the year prior to the index MI, had evidence of substantial frailty (i.e. diagnoses for paralysis, Parkinson's disease, bed sores) in the year prior to the index event [58], did not survive the index hospitalization, or died within 60 days of index discharge. Beneficiaries were also excluded from this study if they did not have a community designated index discharge destination code (Appendix Table 2) or had a length of hospital stay greater than 153 days.

The 12 months before the index hospitalization period was used to define baseline covariates (Figure 5.1). The index hospital period began with the MI admission date and concluded at discharge after any contiguous transfers to other facilities if applicable. If a beneficiary remained an inpatient by being transferred to another medical facility then the index period ended when the beneficiary was discharged into the community after the final continuous transfer. The use of outpatient cardiac rehabilitation was assessed in the 60-day exposure window following the index hospitalization period. Outcomes were assessed from the end of the 60-day exposure period until December 31, 2009. The institution review board (IRB) at the University of North Carolina at Chapel Hill approved this study. Individual informed consent was waived by the IRB in this secondary data analysis study.

2.2. Measures

Outcomes

The primary outcome for this study was hospital admission for an acute MI identified by ICD9 code 410.xx during the follow-up period. Secondary outcomes were hospitalization for any reason or a major adverse cardiovascular and cerebrovascular event (MACE) defined as a hospital record for acute MI, angina, heart failure, or stroke identified by the following ICD 9 discharge diagnosis codes: 410.xx, 411.1, 428.xx, 430, 431, 432, 433.x1, 434.x1, 435, 436 [59]. We used bone fractures at any location as a negative control outcome (Appendix Table 3). Beneficiaries were administratively censored on December 31, 2009 (end of follow-up). Mortality was defined by the presence of a date of death in Medicare enrollment data.

Cardiac rehabilitation

CR initiation was defined by an occurrence of HCPCS codes 93797 and 93798 in Medicare data within the 60-day exposure period.

Covariates

We identified demographic and clinical characteristics as potential confounders. Information on age and gender was obtained from Medicare enrollment file. The 2010 American Community Survey was used to assess median household income categories (<= $30,000, $30,001-$60,000, $60,001-$100,000, $100,001-$150,000, >=$150,001) at census block group level. Health care utilization during baseline and index hospitalization period was used to define comorbid conditions [59, 80]. The Gagne score, used to measure comorbidity status in the primary analysis, was categorized to eliminate small cell sizes by grouping all values less than zero into a single category, scores of 5 and 6 into a single category, and all values greater than 7 into a

single category [59]. Using the model coefficients reported by Faurot et al, we estimated the probability of diminished daily activities as a proxy for frailty [58]. Additional baseline cardiovascular and frailty related comorbid conditions were investigated as potential confounders (Appendix Table 5). Hospitalization characteristics such as hospital, intensive care unit, and coronary care unit lengths of stay were also considered as potential confounders. Intensive care and coronary care unit stays were dichotomized (any or none) for analysis.

Guideline recommended medication (GRM) utilization during baseline and exposure periods as well as baseline use of other cardiovascular medication were also included in analyses as potential confounders [14, 81]. Guidelines recommend the use of antiplatelet therapy, beta-blockade therapy, angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), and Statins [14]. Prescription claims from Medicare Part D files linked using National Drug Codes (NDCs) and/or generic names of medications to Anatomical Therapeutic Chemical (ATC) codes were used to identify medications of interest for this study. Although platelet inhibitors such as aspirin have multiple indications, we assumed that utilization at prescription strength in this population was for prevention of cardiovascular events.

2.3. Statistical Analysis

Descriptive statistics were used to describe characteristics of the study population. Standardized differences were calculated to detect differences between CR initiators and non-initiators. The number of person years of follow-up, number of events, and the proportion of deaths were also summarized for each exposure group.

Inverse probability of treatment (IPT) weights were computed to adjust for confounding between CR initiation and subsequent cardiovascular hospitalization after index MI. The logistic regression model used to estimate the probability of initiating CR contained a variety of baseline variables identified as potential confounders from subject matter knowledge encoded in directed acyclic graphs (Appendix Table 6). A small subset of these variables were removed from the final model to allow for model convergence. Age and length of hospital stay (LOS) were included in the models as restricted cubic splines with 3 and 4 knots respectively [82]. The distribution of the predicted probabilities from the final logistic regression model was examined for overlap between exposure groups. The final weights used in the analysis of outcomes were calculated by taking the inverse of the probability of treatment conditional on measured covariates stabilized by multiplying by the unconditional probability of treatment (shown below).

$$PTW_i = \frac{\Pr(CR = x)}{\Pr(CR = x \mid \boldsymbol{Z})}$$

The unconditional probability in the numerator is used to reduce the variability in the weights [83]. The same IPT weights were used in the analysis of all study outcomes. In a sensitivity analysis, conditions defined by Elixhauser et.al were used to model comorbidity instead of the Gagne score in computing IPT weights [80]. Standardized differences were calculated to detect differences between CR initiators and non-initiators in IPT weighted populations.

Cumulative incidence of each outcome was estimated using non-parametric cumulative incidence estimators with death treated as a competing event [84]. Cumulative incidence curves for each hospital outcome and the corresponding competing event of death were produced for each outcome separately. The 1-year risk difference and risk ratio between CR initiators and non-initiators were computed from cumulative incidence estimates with and without IPT weight adjustment separately. The 1-year risk difference calculated from IPT weighted cumulative incidence estimators represents the population average treatment effect [85]. We conducted stratified analyses by age group (65 – 74 and 75 – 84 years old), mortality risk (Gagne score <five or ≥5), and exposure period GRM use (0, 1-2, and 3-4). High mortality risk defined as ≥ 17% chance of death within 1 year by Gagne et al. corresponded to scores ≥5. Gray's test was used to test for differences between groups in the stratified analysis [86]. All analyses were completed using SAS 9.4.

3. Results.

We identified 32, 851 beneficiaries who met study criteria. The majority of study participants were male (52.1%), White (88.4%), and the mean age at index MI was 75 (SD 6.0) years old. Cardiac rehabilitation (CR) was initiated differently across several key baseline characteristics such as demographic minority, type of revascularization procedure performed during index hospitalizations, and mean comorbidity score (Table 5.1:). By applying stabilized inverse probability of treatment weights, we were able to eliminate the large measured imbalances between exposure groups. The variables used in the final IPT weighting model included demographic characteristics, baseline conditions, index hospitalization care, and medication use.

Only 21% of study participants initiated CR during the exposure period. Initiators participated in an average of 10.6 sessions during the exposure period. In the weighted population, CR initiators contributed 9,758 person years of follow-up time for MI hospitalization outcome and had an observed mortality rate of 2.1 beneficiaries per 100 person years while CR non-initiators contributed 35,672 person years of follow-up time and had an observed mortality rate of 3.5 beneficiaries per 100 person years (data not shown). The observed mortality rate was lower in the CR initiator group than in the non-initiator group for all outcomes studied (Table 5.2:). As expected, there were more all-cause admission events than MACE events than MI events.

Plots of the cumulative incidence during follow-up (Figure 5.2) reveal that CR initiators had a lower risk of hospitalization (top row) and competing death event (bottom row) than non-initiators even at 90-days post discharge (30 days of follow-up). While the risk of MI hospitalization was similar in scale to the competing risk of all-cause death in this study, the risk of MI admission was slightly higher than the risk of death during follow-up. Confounding adjustment by IPT weighting attenuated differences between exposure groups for MI hospitalization and death events (Table 5.2:). Side by side depiction of adjusted cumulative incidence curves for MI, MACE, and all-cause admission illustrate only a small difference between CR initiators and non-initiators for each of these outcomes (Figure 5.2). This small difference persisted for all three outcomes during follow-up. At 1-year post discharge there was a less than 3% absolute risk reduction in MI (1.0%), MACE (2.4%), and all-cause (2.8%) hospitalizations among CR initiators when compared to non-initiators (Table 5.2:) after adjusting for confounding and the competing risk of death. The small absolute differences had

corresponding risk ratios of 0.81 (0.70, 0.92), 0.87 (0.81, 0.93), and 0.92 (0.89, 0.95) for MI, MACE, and all-cause hospitalization respectively.

We also investigated if there was difference between exposure groups in the risk of each outcome by age group, Gagne score, and exposure period GRM use (Table 5.3:). The negative absolute 1-year risk difference between CR initiators and non-initiators for recurrent MI was similar for each age group. For the all-cause admission outcome, beneficiaries in the older age group had a larger 1-year risk reduction than younger age group. Beneficiaries with a Gagne score ≥5 had approximately 2.5 times the 1-year risk of experiencing study cardiovascular outcomes than beneficiaries with a Gagne score < 5. A negative risk difference between CR initiators and non-initiators was observed for all study outcomes among beneficiaries with a Gagne score < 5 but not the higher Gagne score group. Beneficiaries who had days supply for 1-2 GRMs at day 60 had an insignificant <1% decrease in the 1-year risk of MI between CR initiators and non-initiators but at least a 2% decrease in the 1-year risk of MACE or all-cause admission outcomes. Beneficiaries who had days supply for 3-4 GRMs at day 60 had the highest risk reduction of hospital admission in the GRM stratified analyses regardless of outcome. The sensitivity analysis using the Elixhauser definitions of comorbid conditions produced estimates that were slightly closer to the null than the main analysis but did not change our conclusions (data not shown).

4. Discussion

We examined the association between CR initiation and re-hospitalization following an index MI among older adults. The observed low CR initiation was similar to what has been reported in an earlier study of Medicare beneficiaries with an index MI occurring in 1997 (24%) and was lower than estimates reported by a more recent registry study (32%) [20, 79]. A small difference in absolute measures of 1-year risk of recurrent MI between CR initiators and non-initiators translated into a large relative difference due to the low risk in each group. The observed relative risk of recurrent MI within 1 year of discharge of 0.81 (95% CI 0.70, 0.92) was similar to results reported in a meta-analysis of CR clinical trials by Clark et al. (0.83 95% CI 0.74, 0.94) [4]. The low (<10%) 1-year risk of recurrent MI reported in this study is consistent with a recent randomized clinical trial by West et al. of CR use after MI [78]. While Clark et al reported a statistical difference in recurrent MI between rehabilitation users and controls; West et al concluded there was no difference in risk of recurrent MI between CR users and controls. Based upon the results of this study, we conclude that the small effect that CR has on the 1-year risk of recurrent MI does not have the same public health importance as the effect of CR on the other hospitalization outcomes investigated in this study.

The 1-year risk of MACE admission and all-cause hospitalization was 4 to 7 times greater than the 1-year risk of MI readmission in this study. While the magnitude of the 1-year risk difference was similar between the MACE and all-cause hospitalization outcomes, the relative measure of the difference between CR initiator and non-initiators was different due to difference in the baseline risk of each outcome. In a study of CR participation between 1987 and 2010 of Olmsted County residents, Dunlay et al reported a 20% and 25% decrease in the relative risk of cardiovascular admission and all-cause hospitalization respectively between initiators and non-

initiators [87]. The average follow-up time in the Dunlay study was 7.6 years [87]. With a 1-year hazard ratio of 0.85 (95% CI: 0.79 to 0.91) for MACE admissions, our study supports that a majority of the benefit of CR on cardiovascular admission in MI survivors occurs within the first year of discharge. Similarly, we observed evidence of a decrease in the all-cause admissions, 1-year hazard ratio 0.89 (95%CI: 0.84 to 0.94) but not to the same degree as results reported by Dunlay et al., hazard ratio of 0.75 (95%CI: 0.65 to 0.87).

Stratified analysis in our study showed that older beneficiaries (>75 years olda0 had a greater reduction in the all-cause admission outcome than the cardiovascular outcomes. In addition, those CR initiators with days supply of 3-4 GRMs at day 60 had a lower 1-year risk of each hospitalization outcome than CR initiators with days supply of less medication at day 60. The former observation supports an AHA scientific statement that encourages the use of secondary prevention methods in elderly patients especially those at least 75 years old [88]. The latter observation represents an opportunity for public health intervention since CR participation has also been shown to increase medication adherence [79]. It should also be noted that the risk of each study outcome for CR initiators with days supply of 1-2 medications at day 60 is similar to the risk of that same outcome in CR non-initiators with days supply of 3-4 medications at day 60.

We decided to restrict our study population to beneficiaries who received a revascularization procedure during their index hospitalizations for several reasons. First, previous literature has reported that revascularization is highly associated with referral for CR [23]; therefore, restriction may impose a level of homogeneity of treatment groups that should reduce indication bias. Since we cannot measure which of the non-initiators were also not referred for CR, this restriction eliminates from our risk set a pool of patients who would never initiate because they were never referred. This is not a perfect proxy for referral since we are also removing patients

from our population that were referred. However, this restriction is an imperfect measure of referral and limits the generalizability of our results.

Conducting research using administrative claims data has both limitations and benefits. First, administrative claims data were created for financial purposes not research purposes. While there is some overlap in these objectives, research relevant details are absent from claims data where these objectives begin to diverge. For example, clinical data such as laboratory results, smoking status, and BMI are lacking in administrative data. In this study, we attempted to overcome the presence of this unmeasured confounding using propensity score techniques but realize that residual confounding may still exist in our results. The lack of an association between CR initiation and fracture risk (the negative control outcome) suggested that our study results may not be subject to substantial residual confounding.

We were limited to claims for beneficiaries who were continuously enrolled in Medicare Part D and Medicare Part A and B from 1 year before their index hospitalization until December 31, 2009 or death. By restricting to the continuously covered population, we may be limiting the generalizability of our study findings; however, the size and nature of the population is still of public health importance. There was the potential for misclassification of exposure to GRMs due to use of over the counter aspirin, free medication samples risk [75] and purchase of prescription drugs without filing an insurance claim [74]. Besides over-the-counter aspirin use, generic options of the medication classes included in this study were offered at prices low enough to be regularly purchased using cash without filing a claim. These cash transactions were not captured in our study data. However, we expect the use of these medications to be non-differential with respect to the use of cardiac rehabilitation services.

There are several strengths to this study. Our claims-based analysis is not subject to recall bias since we have documentation on the receipt and timing of health services studied. While filling a prescription does not guarantee that the medication has been taken, it is likely a better measure of medication exposure than definitions by prescriptions written at discharge. Most of the clinical trials of cardiac rehabilitation were small (<300 enrollees) enrolling younger (under the age of 60) predominately male populations, conducted before improvements in secondary prevention medications, and conducted in countries outside the US where access to care is different [77]. The larger sample size than clinical trials, the inclusion of large percentage of women, and focusing on older adults are advantages to this study.

In conclusion, our results suggest that outpatient cardiac rehabilitation may reduce cardiovascular and all-cause hospital admissions 1-year post discharge in elderly MI survivors. However, public health interventions are need to improve the observed low rates of CR initiation among older adults for these benefits to be fully realized in elderly MI survivors.

5. Tables.

Table 5.1: Study Population Characteristics

	Unadjusted			IPT Weighted
	CR Non-Initiators	**CR Initiators**	**Standardized Difference**	**Standardized Difference**
Overall	25,935	6,916		
Demographics				
Mean Age (SD)	75.1 (5.98)	74.2 (5.58)	-0.157	0.001
Female	12,788 (49.3%)	2,933 (42.4%)	-0.139	-0.013
Minority	3,473 (13.4%)	346 (5.0%)	-0.293	0.038
Index Hospitalizations				
Revascularization				
Angioplasty	21,358 (82.4%)	5,101 (73.8%)	-0.209	-0.007
CABG	4,741 (18.3%)	2,004 (29.0%)	0.254	0.015
Stent	19,539 (75.3%)	4,690 (67.8%)	-0.167	-0.011
Cardiogenic Shock	1,213 (4.7%)	318 (4.6%)	-0.004	0.005
Any ICU Stay	15,477 (59.7%)	4,265 (61.7%)	0.041	0.009
Any CCU Stay	12,311 (47.5%)	3,374 (48.8%)	0.026	0.007
Hospital Transfer Group				
0	19,605 (75.6%)	5,725 (82.8%)	0.178	0.003
1	5,080 (19.6%)	1,026 (14.8%)	-0.126	0.001
>2	1,250 (4.8%)	165 (2.4%)	-0.131	-0.008
Baseline Medications				
Any Baseline Coverage Gap				
Doughnut Hole	7,601 (29.3%)	1,421 (20.5%)	-0.204	0.010
Baseline Comorbidities				
Gagne Comorbidity Score				
Mean (SD)	1.7 (2.22)	1.0 (1.79)	-0.322	0.015
Comorbid Conditions				
Hyperlipidemia	18,509 (71.4%)	5,275 (76.3%)	0.112	-0.007
Osteoporosis or Osteoarthritis	6,319 (24.4%)	1,656 (23.9%)	-0.010	0.005
Hypotension	2,218 (8.6%)	562 (8.1%)	-0.015	-0.007
Hypertension	21,664 (83.5%)	5,486 (79.3%)	-0.108	-0.002
Uncomplicated Diabetes	10,727 (41.4%)	2,271 (32.8%)	-0.177	0.013
Congestive Heart Failure	8,947 (34.5%)	1,629 (23.6%)	-0.243	-0.007
Cardiac Arrhythmia	7,992 (30.8%)	2,007 (29.0%)	-0.039	0.035
Chronic Pulmonary Disease	7,844 (30.2%)	1,481 (21.4%)	-0.203	0.018
Peripheral Vascular Disease	5,449 (21.0%)	960 (13.9%)	-0.189	0.025
Valvular Disease	4,756 (18.3%)	1,153 (16.7%)	-0.044	-0.011
Complicated Diabetes	3,147 (12.1%)	502 (7.3%)	-0.165	0.013

	Unadjusted			IPT Weighted
	CR Non-Initiators	**CR Initiators**	**Standardized Difference**	**Standardized Difference**
Cancer	2,745 (10.6%)	753 (10.9%)	0.010	0.007
Cerebrovascular Disease	2,588 (10.0%)	471 (6.8%)	-0.114	-0.011
Rheumatic Disease	1,242 (4.8%)	326 (4.7%)	-0.004	0.006
Renal Disease	1,210 (4.7%)	139 (2.0%)	-0.148	0.017
Metastatic Carcinoma	294 (1.1%)	49 (0.7%)	-0.045	-0.011
Day 60 Medication				
GRM Group				
0	1,651 (6.4%)	235 (3.4%)	-0.138	-0.046
1-2	7,695 (29.7%)	1,896 (27.4%)	-0.050	0.017
3-4	16,589 (64.0%)	4,785 (69.2%)	0.111	0.005

Note: IPT – Inverse Probability of Treatment Weighted. CR – Outpatient Cardiac Rehabilitation. SD – Standard Deviation. CABG – Coronary Artery Bypass Grafting. ICU – Intensive Care Unit. CCU – Cardiac Care Unit. GRM – Guideline Recommended Medications.

Table 5.2: Summary of Person-Time on Study, Risk, Risk Difference, and Relative Risk of Study Outcomes at 1-Year Post-MI for Outpatient Cardiac Rehabilitation (CR) Initiators verses Non-Initiators

Outcome	Cardiac Rehab	Person years (PY)	Events	Deaths	Mortality Rate (/100 PY)	Unadjusted Risk (%)	Unadjusted Risk Difference	Adjusted Risk (%)	Adjusted Risk Difference	Adjusted Risk Ratio
MI	Non-Initiators	35,353.51	1,900	1,362	3.9	5.6 (5.3, 5.9)		5.2 (5.0, 5.5)		
	Initiators	9,960.09	250	127	1.3	2.7 (2.3, 3.1)	-2.9 (-3.0, -2.8)	4.2 (3.5, 5.1)	-1.0 (-1.5, -0.4)	0.81 (0.70, 0.92)
MACE	Non-Initiators	28,638.04	5,591	958	3.3	19.2 (18.7, 19.8)		18.0 (17.6, 18.4)		
	Initiators	8,807.76	960	109	1.2	11.7 (10.9, 12.5)	-7.5 (-7.8, -7.3)	15.7 (14.3, 17.2)	-2.4 (-3.3, -1.2)	0.87 (0.81, 0.93)
All-Cause Admission	Non-Initiators	21,466.26	8,462	725	3.4	34.6 (33.9, 35.4)		33.2 (32.5, 33.8)		
	Initiators	7,020.35	1,947	92	1.3	26.0 (24.9, 27.2)	-8.6 (-9.0, -8.1)	30.4 (28.8, 32.1)	-2.8 (-3.7, -1.7)	0.92 (0.89, 0.95)
Fracture	Non-Initiators	36,915.43	804	1,466	4.0	2.1 (2.0, 2.3)		2.0 (1.8, 2.1)		
	Initiators	10,168.98	142	136	1.3	1.4 (1.1, 1.7)	-0.8 (-0.9, -0.6)	1.9 (1.4, 2.4)	-0.1 (-0.4, 0.3)	0.94 (0.78, 1.15)

Note: MI – Myocardial Infarction. MACE - major adverse cardiovascular and cerebrovascular event (MI, angina, heart failure, or stroke)

Table 5.3: Stratified Analysis of Risk, Risk Difference, and Relative Risk of Study Outcomes at 1-Year Post-MI for Outpatient Cardiac Rehabilitation (CR) Initiators verses Non-Initiators

	CR Non-Initiators Risk (%)	CR Initiators Risk (%)	Risk Difference	Risk Ratio
MI				
Age Group				
Age 65-74 years	4.6 (4.2, 5.0)	3.7 (2.8, 4.9)	-0.8 (-1.4, -0.0)	0.8 (0.66, 1.00)
Age 75-84 years	5.8 (5.4, 6.2)	4.7 (3.4, 6.2)	-1.1 (-2.1, -0.0)	0.8 (0.62, 0.99)
Morbidity Risk				
Gagne Score < 5	4.7 (4.4, 5.0)	3.5 (2.8, 4.1)	-1.2 (-1.6, -0.8)	0.7 (0.64, 0.83)
Gagne Score >=5	10.6 (9.5, 11.9)	11.2 (6.2, 17.1)	0.6 (-3.3, 5.3)	1.1 (0.65, 1.44)
Day 60 GRM Group				
0	5.2 (4.1, 6.3)	7.0 (1.3, 15.3)	1.8 (-2.8, 9.0)	1.3 (0.33, 2.43)
1-2	5.7 (5.2, 6.2)	4.8 (3.0, 6.5)	-0.9 (-2.1, 0.3)	0.8 (0.59, 1.05)
3-4	5.0 (4.7, 5.4)	3.8 (2.9, 4.5)	-1.3 (-1.8, -0.9)	0.8 (0.62, 0.84)
MACE				
Age Group				
Age 65-74 years	15.4 (14.8, 16.0)	13.6 (12.0, 15.4)	-1.8 (-2.8, -0.6)	0.9 (0.81, 0.96)
Age 75-84 years	20.0 (19.2, 20.9)	18.0 (15.6, 21.3)	-2.0 (-3.6, 0.4)	0.9 (0.81, 1.02)
Morbidity Risk				
Gagne Score < 5	16.3 (15.8, 16.8)	13.5 (12.6, 14.7)	-2.7 (-3.2, -2.1)	0.8 (0.80, 0.88)
Gagne Score >=5	37.9 (35.9, 39.9)	36.1 (26.4, 45.7)	-1.7 (-9.5, 5.8)	1.0 (0.74, 1.15)
Day 60 GRM Group				
0	20.0 (18.0, 22.0)	21.5 (12.8, 30.7)	1.5 (-5.1, 8.7)	1.1 (0.71, 1.40)
1-2	19.1 (18.1, 19.9)	17.1 (14.7, 19.6)	-2.0 (-3.4, -0.3)	0.9 (0.81, 0.98)
3-4	17.4 (16.8, 18.0)	14.6 (12.7, 16.5)	-2.8 (-4.1, -1.5)	0.8 (0.76, 0.92)
All-Cause Admission				
Age Group				
Age 65-74 years	29.9 (29.0, 30.9)	28.7 (26.7, 31.3)	-1.2 (-2.3, 0.4)	1.0 (0.92, 1.01)
Age 75-84 years	35.7 (34.6, 36.6)	32.6 (28.9, 35.4)	-3.0 (-5.7, -1.2)	0.9 (0.84, 0.97)
Morbidity Risk				
Gagne Score < 5	31.3 (30.7, 31.9)	27.7 (26.0, 28.9)	-3.6 (-4.7, -3.0)	0.9 (0.85, 0.91)
Gagne Score >=5	56.6 (54.0, 58.8)	57.0 (46.9, 65.8)	0.4 (-7.1, 7.0)	1.0 (0.87, 1.12)
Day 60 GRM Group				
0	33.0 (30.1, 36.0)	39.7 (28.5, 51.4)	6.7 (-1.6, 15.4)	1.2 (0.95, 1.43)
1-2	34.1 (32.5, 35.4)	31.8 (28.4, 35.0)	-2.3 (-4.1, -0.4)	0.9 (0.87, 0.99)
3-4	32.8 (32.0, 33.6)	29.1 (26.8, 31.1)	-3.7 (-5.2, -2.5)	0.9 (0.84, 0.93)

Note: MI – Myocardial Infarction. MACE – major adverse cardiovascular and cerebrovascular event (MI, angina, heart failure, or stroke). GRM Guideline Recommended Medications.

6. Figures

Figure 5.1: Study Design

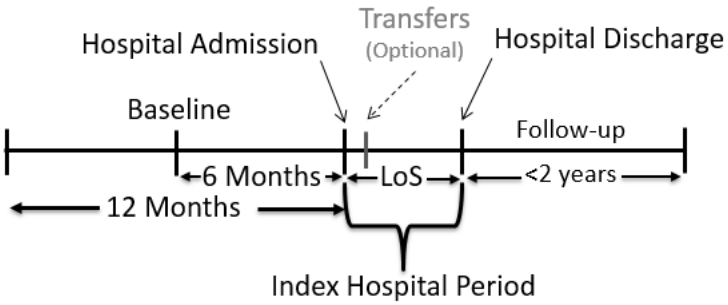
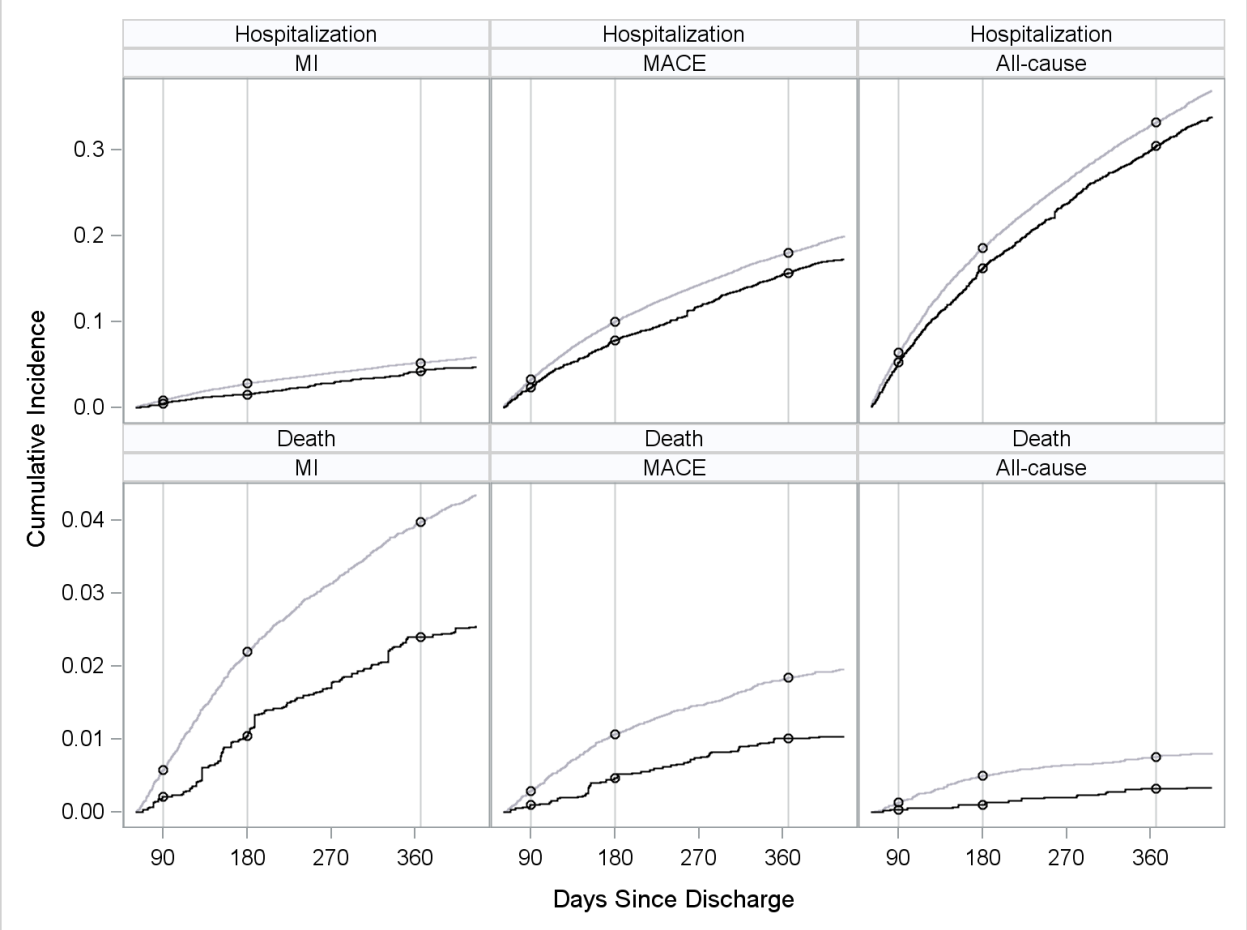


Figure 5.2: Inverse Probability of Treatment Weighted Cumulative Incidence of All Study Outcomes and Competing Risk of Death in Outpatient Cardiac Rehabilitation Initiators compared to Non-Initiators



Note: MACE - major adverse cardiovascular and cerebrovascular event (MI, angina, heart failure, or stroke

CHAPTER 6: CONCLUSIONS AND PUBLIC HEALTH IMPACT

The intent of this dissertation was to investigate the use of secondary prevention guideline recommendations among Medicare beneficiaries. This was accomplished in two steps. First, the initiation of cardiac rehabilitation and the concurrent use of guideline recommended medications after an index myocardial infarction were summarized in the comparison of methods to account for death before the outcome of interest when conducting survival data analysis. This manuscript described the less than optimal adoption of guideline recommendations. By 1-year post-MI discharge, beneficiaries were more likely to fill prescriptions for concordant guideline medications (51.4%) than participate in cardiac rehabilitation (14.2%) before death. In addition, the proportion of CR initiators nearly doubled between 30 days post discharge and 90 days post discharge. This result has implications for outcomes research with CR initiation as an exposure when employing fixed exposure windows in the design. Restricting the study cohort by survival reduced the population at risk while censoring by death assumed that patients who die could still go on to participate with therapy. These methods of accounting for death resulted in higher estimates of post-MI CR and GRM use then competing risk estimates. In studies where mortality is more common, restricting the study to patients who survive may affect generalizability and may introduce some survivor bias in the results. In these settings, competing risk approaches would be preferable. Because clinical trials and observational studies provided as support for guideline recommendations focused on the efficacy of each component individually, this study adds to existing knowledge by summarizing exposure to multiple guideline components after index hospitalization discharge.

The second manuscript summarized the relationship between initiation of cardiac rehabilitation and hospital admission following an index MI among older adults having a revascularization procedure. The 1-year risk of cardiovascular or all-cause hospitalization was 4 to 7 times greater than the 1-year risk of MI readmission in this study. The risk difference between CR initiators and non-initiators for cardiovascular and all-cause hospitalization outcomes following an index MI were small but clinically significant. In the stratified analysis, marginally greater benefit of CR initiation on these outcomes was observed in beneficiaries that were older (75 to 85 years old), healthier (Gagne score <5), and more compliant with guideline medications (at least 1) compared to beneficiaries 65 to 74, Gagne score ≥ 5, or not taking any guideline recommended medication respectively.

By investigating use of both health care services and evidence based medications using competing risks methods of survival data analysis, this dissertation adds to the knowledge regarding the use of secondary prevention methods in an elderly US population. The size and nature of the population involved in this investigation is of public health importance since previous studies of secondary prevention methods focused on younger male patients and may have overestimated the effects of these recommendations on non-fatal outcomes when death was not properly analyzed. Results from this dissertation support that outpatient cardiac rehabilitation reduces cardiovascular and all-cause hospital admissions 1-year post discharge in elderly MI survivors. However, the potential benefit to society from using this therapy is not fully realized due to the observed low adoption of guideline recommendations among Medicare beneficiaries. Results from this dissertation can be used in public health interventions to inform patients and practitioners of the benefits of following guideline recommendations and encourage referral and participation in cardiac rehabilitation among older adult MI survivors.

APPENDIX

Appendix Table 1: Summary of secondary prevention guideline recommendations ([10, 11])

Component	Intervention Recommendation	Class
NUTRITION COUNSELING AND WEIGHT MANAGEMENT Goal: Body mass index: 18.5 to 24.9 kg/m^2 Waist circumference: men <40 inches, Women <35 inches	• Assess body mass index and/or waist circumference on each visit and consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a body mass index between 18.5 and 24.9 kg/m^2. • If waist circumference (measured horizontally at the iliac crest) is ≥35 inches in women and ≥40 inches in men, initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated. • The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment.	I (B) I (B) I (B)
DIABETES MANAGEMENT Goal: HbA1c <7%	• Initiate lifestyle and pharmacotherapy to achieve near-normal HbA1c. • Begin vigorous modification of other risk factors (e.g., physical activity, weight management, blood pressure control, and cholesterol management as recommended above). • Coordinate diabetic care with patient's primary care physician or endocrinologist.	I (B) I (B) I (C)

†Non-HDL-C = total cholesterol minus HDL-C. ‡Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

§When LDL-lowering medications are used, obtain at least a 30% to 40% reduction in LDL-C levels. If LDL-C <70 mg/dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C <70 mg/dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of >50% in LDL-C levels by either statins or LDL-C–lowering drug combinations.

¶The combination of high-dose statin fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.

#Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is relatively contraindicated when triglycerides are >200 mg/dL.

Ⱶ Standard dose of statin with ezetimibe, bile acid sequestrant, or niacin. **Creatinine should be <2.5 mg/dL in men and <2.0 mg/dL in women. ††Potassium should be <5.0 mEq/L.

Component	Intervention Recommendation	Class
BLOOD PRESSURE CONTROL Goal: <140/90 mm Hg or <130/80 mm Hg if patient has diabetes or chronic kidney disease	For all patients: • Initiate or maintain lifestyle modification—weight control; increased physical activity; alcohol moderation; sodium reduction; and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products For patients with blood pressure >140/90 mm Hg (or >130/80 mm Hg for individuals with diabetes or chronic kidney disease): • As tolerated, add blood pressure medication, treating initially with ß-blockers and/or ACE inhibitors, with addition of other drugs such as thiazides as needed to achieve goal blood pressure [For compelling indications for individual drug classes in specific vascular diseases, see Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)]	I (B) I (A)

†Non-HDL-C = total cholesterol minus HDL-C. ‡Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

§When LDL-lowering medications are used, obtain at least a 30% to 40% reduction in LDL-C levels. If LDL-C <70 mg/dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C <70 mg/dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of >50% in LDL-C levels by either statins or LDL-C–lowering drug combinations.

¶The combination of high-dose statin fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.

#Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is relatively contraindicated when triglycerides are >200 mg/dL.

Ⱡ Standard dose of statin with ezetimibe, bile acid sequestrant, or niacin. **Creatinine should be <2.5 mg/dL in men and <2.0 mg/dL in women. ††Potassium should be <5.0 mEq/L.

Component	Intervention Recommendation	Class
SMOKING CESSATION COUNSELING Goal: Complete cessation. No exposure to environmental tobacco smoke.	• Ask about tobacco use status at every visit • Advise every tobacco user to quit • Assess the tobacco user's willingness to quit • Assist by counseling and developing a plan for quitting • Arrange follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion) • Urge avoidance of exposure to environmental tobacco smoke at work and home	I (B) I (B) I (B) I (B) I (B) I (B)
LIPID MANAGEMENT Goal: LDL-C <100 mg/dL If triglycerides are ≥200 mg/dL, non-HDL-C should be <130 mg/dL†	For all patients: • Reduce intake of saturated fats (to <7% of total calories), trans-fatty acids, and cholesterol (to <200 mg/d). • Adding plant stanol/sterols (2 g/d) and viscous fiber (>10 g/d) will further lower LDL-C • Promote daily physical activity and weight management • Encourage increased consumption of omega-3 fatty acids in the form of fish‡ or in capsule form (1 g/d) for risk reduction. For treatment of elevated triglycerides, higher doses are usually necessary for risk reduction.	I (B) I (B) IIb (B)

†Non-HDL-C = total cholesterol minus HDL-C. ‡Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

§When LDL-lowering medications are used, obtain at least a 30% to 40% reduction in LDL-C levels. If LDL-C <70 mg/dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C <70 mg/dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of >50% in LDL-C levels by either statins or LDL-C–lowering drug combinations.

¶The combination of high-dose statin fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.

#Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is relatively contraindicated when triglycerides are >200 mg/dL.

ΠStandard dose of statin with ezetimibe, bile acid sequestrant, or niacin. **Creatinine should be <2.5 mg/dL in men and <2.0 mg/dL in women. ††Potassium should be <5.0 mEq/L.

Component	Intervention Recommendation	Class
LIPID MANAGEMENT Goal: LDL-C <100 mg/dL If triglycerides are ≥200 mg/dL, non-HDL-C should be <130 mg/dL†	For lipid management: Assess fasting lipid profile in all patients, and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. For hospitalized patients, initiate lipid-lowering medication as recommended below before discharge according to the following schedule • LDL-C should be <100 mg/dL and • Further reduction of LDL-C to <70 mg/dL is reasonable • If baseline LDL-C is ≥100 mg/dL, initiate LDL-lowering drug therapy § • If on-treatment LDL-C is ≥100 mg/dL, intensify LDL-lowering drug therapy (may require LDL-lowering drug combination‖) • If baseline LDL-C is 70 to 100 mg/dL, it is reasonable to treat to LDL-C <70 mg/dL • If triglycerides are 200 to 499 mg/dL, non-HDL-C should be <130 mg/dL, and • Further reduction of non-HDL-C to <100 mg/dL is reasonable • Therapeutic options to reduce non-HDL-C are: o More intense LDL-C–lowering therapy or o Niacin¶ (after LDL-C–lowering therapy) or Fibrate therapy# (after LDL-C–lowering therapy) • If triglycerides are 500 mg/dL#, therapeutic options to prevent pancreatitis are fibrate¶ or niacin¶ before LDL-lowering therapy; and treat LDL-C to goal after triglyceride-lowering therapy. Achieve non-HDL-C <130 mg/dL if possible.	I (A) IIa (A) I (A) I (A) IIa (B) I (B) IIa (B) I (B) IIa (B) I (C)

†Non-HDL-C = total cholesterol minus HDL-C. ‡Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

§When LDL-lowering medications are used, obtain at least a 30% to 40% reduction in LDL-C levels. If LDL-C <70 mg/dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C <70 mg/dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of >50% in LDL-C levels by either statins or LDL-C–lowering drug combinations.

¶The combination of high-dose statin fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.

#Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is relatively contraindicated when triglycerides are >200 mg/dL.

‖Standard dose of statin with ezetimibe, bile acid sequestrant, or niacin. **Creatinine should be <2.5 mg/dL in men and <2.0 mg/dL in women. ††Potassium should be <5.0 mEq/L.

Component	Intervention Recommendation	Class
ß-BLOCKERS	• Start and continue indefinitely in all patients who have had myocardial infarction, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated • Consider chronic therapy for all other patients with coronary or other vascular disease or diabetes unless contraindicated	I (A) IIa (C)
RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM BLOCKERS	<u>ACE inhibitors:</u> • Start and continue indefinitely in all patients with left ventricular ejection fraction ≤ 40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated • Consider for all other patients • Among lower-risk patients with normal left ventricular ejection fraction in whom cardiovascular risk factors are well controlled and revascularization has been performed, use of ACE inhibitors may be considered optional <u>Angiotensin receptor blockers:</u> • Use in patients who are intolerant of ACE inhibitors and have heart failure or have had a myocardial infarction with left ventricular ejection fraction ≤ 40% • Consider in other patients who are ACE inhibitor intolerant • Consider use in combination with ACE inhibitors in systolic-dysfunction heart failure <u>Aldosterone blockade:</u> • Use in post–myocardial infarction patients, without significant renal dysfunction** or hyperkalemia††, who are already receiving therapeutic doses of an ACE inhibitor and ß-blocker, have a left ventricular ejection fraction ≤ 40%, and have either diabetes or heart failure	 I (A) I (B) IIa (B) I (A) I (B) IIb (B) I (A)

†Non-HDL-C = total cholesterol minus HDL-C. ‡Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

§When LDL-lowering medications are used, obtain at least a 30% to 40% reduction in LDL-C levels. If LDL-C <70 mg/dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C <70 mg/dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of >50% in LDL-C levels by either statins or LDL-C–lowering drug combinations.

¶The combination of high-dose statin fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.

#Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is relatively contraindicated when triglycerides are >200 mg/dL.

Ⱶ Standard dose of statin with ezetimibe, bile acid sequestrant, or niacin. **Creatinine should be <2.5 mg/dL in men and <2.0 mg/dL in women. ††Potassium should be <5.0 mEq/L.

Component	Intervention Recommendation	Class

ANTIPLATELET AGENTS/ ANTI-COAGULANTS	• Start aspirin 75 to 162 mg/d and continue indefinitely in all patients unless contraindicated
	  ○ For patients undergoing coronary artery bypass grafting, aspirin should be started within 48 hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg/d appear to be efficacious. Doses higher than 162 mg/d can be continued for up to 1 year.
	• Start and continue clopidogrel 75 mg/d in combination with aspirin for up to 12 months in patients after acute coronary syndrome or percutaneous coronary intervention with stent placement (≥1 month for bare metal stent, ≥3 months for sirolimus-eluting stent, and ≥6 months for paclitaxel-eluting stent)
	  ○ Patients who have undergone percutaneous coronary intervention with stent placement should initially receive higher-dose aspirin at 325 mg/d for 1 month for bare metal stent, 3 months for sirolimus-eluting stent, and 6 months for paclitaxel-eluting stent.
	• Manage warfarin to international normalized ratio=2.0 to 3.0 for paroxysmal or chronic atrial fibrillation or flutter, and in post–myocardial infarction patients when clinically indicated (e.g., atrial fibrillation, left ventricular thrombus).
	• Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely.
		I (A)
		I (B)
		I (B)
		I (B)
		I (A)
		I (B)

INFLUENZA VACCINATION	• Patients with cardiovascular disease should have an influenza vaccination.	I (B)

†Non-HDL-C = total cholesterol minus HDL-C. ‡Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

§When LDL-lowering medications are used, obtain at least a 30% to 40% reduction in LDL-C levels. If LDL-C <70 mg/dL is the chosen target, consider drug titration to achieve this level to minimize side effects and cost. When LDL-C <70 mg/dL is not achievable because of high baseline LDL-C levels, it generally is possible to achieve reductions of >50% in LDL-C levels by either statins or LDL-C–lowering drug combinations.

¶The combination of high-dose statin fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.

#Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrant is relatively contraindicated when triglycerides are >200 mg/dL.

Standard dose of statin with ezetimibe, bile acid sequestrant, or niacin. **Creatinine should be <2.5 mg/dL in men and <2.0 mg/dL in women. ††Potassium should be <5.0 mEq/L.

Appendix Table 2: Discharge Destination Codes

Home Codes	**Description**
01	Discharged to home/self-care.
06	Discharged/transferred to home care of organized home health service organization.
07	Left against medical advice or discontinued care.
50	Hospice - home

Appendix Table 3: Fracture Related ICD-9 Discharge Codes

Anatomical Location	**Specific fracture sites**	**Algorithm**
Hip	Femoral neck: - Transcervical fracture, closed - Pertrochanteric fracture, closed - Unspecified part of neck of femur, closed (Hip NOS, Neck of femur, NOS) Pathologic fracture of neck of femur	**Inpatient primary** or **secondary** diagnosis codes [substr4(8200, 8202, 8208) or 73314] **OR** **Carrier line or outpatient claim in any position** with HCPCS in (27230-27248) and diagnosis code [substr4(8200, 8202, 8208) or 73314]
Pelvis-closed	- Acetabulum, closed - Pubis, closed - Other specified part, closed - Unspecified, closed	**Inpatient primary** or **secondary** diagnosis code in [substr4 8080, 8082, 8084, 8088] **OR** **Carrier line or outpatient** claim **in any position** with HCPCS in (27193-27194, 27215-27218, 27220, 27222, 27226-27228) and diagnosis code in [substr4 8080, 8082, 8084, 8088]

Anatomical Location	**Specific fracture sites**	**Algorithm**
Leg-closed other than hip, *not including knee or ankle*	Fracture of other and unspecified parts of femur - Shaft or unspecified part, closed - Lower end, closed (distal end) Fracture of patella Fracture of tibia and fibula - Upper end, closed - Shaft, closed - Unspecified part, closed (Lower leg NOS) Pathologic fracture of other specified part of femur (i.e. other than femoral neck) Pathologic fracture of tibia and fibula (excluding ankle NOS)	**Inpatient primary** or **secondary** diagnosis code in [substr4(8210, 8212, 8220, 8230, 8232, 8238), 73315, 73316] **OR** **Carrier line or outpatient** claim **in any position** with HCPCS in (27500-27514, 27530-27536, 27750-27759, 27780-27784, 27824-27828) and diagnosis code in [substr4(8210, 8212, 8220, 8230, 8232, 8238), 73315, 73316]
Ankle	Fracture of ankle - Medial malleolus, closed (Tibia involving ankle, malleolus) - Lateral malleolus, closed (Fibular involving ankle, malleolus) - Bimalleolar, closed (Dupuytren's fracture, fibula Pott's fracture) - Trimalleolar, closed (Lateral and medial malleolus with anterior or posterior lip) - Unspecified, closed (Ankle NOS)	**Inpatient primary** or **secondary** diagnosis code in [substr3(8240, 8242, 8244, 8246, 8248)] **OR** **Carrier line or outpatient** claim **in any position** with HCPCS in (27760, 27762, 27766, 27786, 27788, 27792, 27808, 27810, 27814, 27816, 27818, 27822, 27823, 28430, 28435, 28436, 28445 (includes talus)) and diagnosis code in [substr3(8240, 8242, 8244, 8246, 8248)]
Distal forearm	Fracture of radius and ulna - Lower end, closed (distal end) Pathologic fracture of distal radius and ulna (Wrist NOS)	**Inpatient primary** or **secondary** diagnosis code in [substr4(8134), 73312)] **OR** **Carrier line or outpatient** claim **in any position** with HCPCS in (25600, 25605, 25611, 25620, 25650, 25651, 25652 (includes ulnar styloid)) and diagnosis code in [substr4(8134), 73312)]

Anatomical Location	**Specific fracture sites**	**Algorithm**
Radius/ulna-other	Fracture of radius and ulna - Upper end, closed (proximal end) - Shaft, closed - Unspecified part, closed	**Inpatient primary** or **secondary** diagnosis code in [substr3(8130, 8132, 8138)] **OR** **Carrier line or outpatient** claim **in any position** with HCPCS in (24650, 24655, 24665, 24666, 24670, 24675, 24685, 25500, 25505, 25515, 25520, 25525, 25526, 25530, 25535, 25545, 25560, 25565, 25574, 25575) and diagnosis code in [substr3(8130, 8132, 8138)]
Humerus-closed	Fracture of humerus - Upper end, closed - Shaft or unspecified part, closed - Lower end, closed (distal end of humerus, elbow) Pathologic fracture of humerus	**Inpatient primary** or **secondary** diagnosis code in [substr4(8120, 8122, 8124), 73311] **OR** **Carrier line or outpatient** claim **in any position** with HCPCS in (23600, 23605, 23615, 23616, 23520, 23625, 23630, 23665, 24500, 24505, 24515, 24516, 24530, 24535, 24538, 24545, 24546, 24560, 24565, 24566, 24575, 24576, 24577, 24579, 24582) and diagnosis code in [substr4(8120, 8122, 8124), 73311]
Clavicle-closed	Fracture of clavicle - Closed	**Inpatient primary** or **secondary** diagnosis code in [substr4(8100)] **OR** **Carrier line or outpatient** claim **in any position** with HCPCS in (23500, 23505, 23515) and diagnosis code in [substr4(8100)]

Anatomical Location	**Specific fracture sites**	**Algorithm**
Vertebral	Fracture of vertebral column without mention of spinal cord injury - Cervical, closed - Dorsal, thoracic (closed) - Lumbar, closed - Sacrum and Coccyx, closed - Unspecified, closed Fracture of vertebral column with spinal cord injury - Cervical, closed - Dorsal, thoracic (closed) - Lumbar, closed - Sacrum and Coccyx, closed - Unspecified, closed	**Inpatient primary or secondary** diagnosis code in [substr3(8050, 8052, 8054, 8056, 8058, 8060, 8062, 8064, 8066, 8068), 73313] **OR** **Carrier line or outpatient** claim **in any position** with HCPCS in (22520, 22521, 22522, 76012, 76013, 22305, 22310, 22315, 22318, 22319, 22325, 22326, 22327, 22328, 22523, 22524, 22525, S2360, S2361, S2362, S2363) and diagnosis code in [substr3(8050, 8052, 8054, 8056, 8058, 8060, 8062, 8064, 8066, 8068), 73313]

Appendix Table 4: Revascularization Codes

Revascularization [89, 90]	CABG: ICD-9-CM procedure codes 36.1-36.19; CPT codes 33510-33523, 33530-33536; Stent: ICD-9-CM procedure codes 36.06-36.07,36.09; HCPCS codes 92980, 92981, G0290, G0291; Angioplasty: ICD-9-CM procedure codes 00.66, 36.01-36.03, 36.05; CPT codes 92982, 92984,92995, 92996; Thrombolytic Agents: ICD-9-CM procedure codes 36.04, 99.10 HCPCS 36593;

Appendix Table 5: Additional Baseline Comorbid Conditions

Description	**ICD-9 Code**
Cardiogenic Shock (index hospitalizations only)	785.51
Hyperlipidemia	272.*
Hypotension	458.*
Gastrointestinal Bleed	578.*
Osteoporosis	733.0*
Osteoarthritis	715.*

[23, 91]

Appendix Table 6: Potential Confounders

Measured:	Unmeasured:
Age, Gender, Race	Marital Status
SES (Income)	Educational Attainment
Revascularization	Rehab proximity
Functional Status	Referring Physician
Mental Status	
Medication Use	
Comorbid conditions	
Insurance Coverage	

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